Risk Factors for Venous Thromboembolism

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In memory of

my mother, Jeanette Parkin

and

a wonderful friend, Angela Buonocore

ABSTRACT

Background

Many risk factors for venous thromboembolism have been identified, but two particular exposures — the use of combined oral contraceptives and long-distance air travel — have generated considerable concern in recent years. In contrast, a possible link between venous thromboembolism and a third exposure — the use of psychotropic drugs — was first raised in the 1950s, but has received surprisingly little attention. Information about all three exposures and the risk of fatal events is limited. These risks were examined in three inter-related national population-based studies.

Methods

The underlying study population included all men and women aged 15 – 59 years who died in New Zealand between 1990 and 2000, for whom the underlying cause of death was pulmonary embolism.

The potential associations between fatal pulmonary embolism and the use of oral contraceptives and psychotropic drugs were explored in a general practice records-based case-control study. Non-users were the reference category for all analyses. Contraceptive supply data were used to estimate the absolute risk of death from pulmonary embolism in users of oral contraceptives.

A second case-control study, in which computer-assisted telephone interviews were undertaken with the next of kin of cases who had been resident in New Zealand, and with sex and age-matched controls randomly selected from the electoral roll, investigated the possible association between long-distance air travel and fatal pulmonary embolism.

Finally, the absolute risk of dying from pulmonary embolism following a long-distance flight was estimated in a descriptive study based on official migration data and deaths in recent air travellers.

Results

The adjusted odds ratio for use of any oral contraceptive in the three months before the index date (the onset of the fatal episode) was 13.1 (95% CI 4.4 – 39.0). The odds ratio for formulations containing desogestrel and gestodene was about three times higher than the point estimate for levonorgestrel products; preparations containing cyproterone acetate appeared to carry the highest risk. The estimated absolute risk of fatal pulmonary embolism in current users of oral contraceptives was 10.5 (95% CI 6.2 – 16.6) per million woman-years.

The adjusted odds ratio for current use of any antipsychotic was 13.3 (95% CI 2.3 – 76.3). Low-potency antipsychotics carried a 20-fold increase in risk; thioridazine was the main drug involved. Antidepressant use was also associated with a significantly increased risk (adjusted odds ratio 4.9 [95% CI 1.1 – 22.5]).

Compared with non-travellers, people who had undertaken a flight of more than eight hours' duration in the preceding four weeks were eight times more likely to die from pulmonary embolism (odds ratio 7.9 [95% CI 1.1 – 55.1]). The absolute risk of fatal pulmonary embolism following air travel of more than eight hours was 1.3 (95% CI 0.4 – 3.0) per million arrivals.

Conclusions

The present research was the first to have estimated the relative risks of fatal pulmonary embolism in relation to three exposures: oral contraceptive use in a population in which preparations containing desogestrel and gestodene preparations were widely used, conventional antipsychotics, and long-distance air travel. The findings were consistent with previous, and subsequent, studies of non-fatal events. Increased risks of fatal pulmonary embolism in users of antidepressants, and in people with an intellectual disability, have not been described previously and warrant further investigation. Referral and diagnostic biases are very unlikely in these studies of fatal events, and other types of bias and possible confounding are considered unlikely explanations for the findings.

PREFACE

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TABLE OF CONTENTS

VOLUME 1

VOLUME 2

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CSM	Committee on Safety of Medicines
CT	Computed tomography
GPRD	General Research Database
kg	Kilograms
m	Metres
mg	Milligrams
µg	Micrograms
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

PART I OVERVIEW

CHAPTER 1 INTRODUCTION

1.1 PREAMBLE

Contemporary insight into the natural history of deep vein thrombosis and pulmonary embolism (collectively referred to as venous thromboembolism) derives from pioneering work undertaken by the nineteenth century pathologist, Rudolf Virchow. From a lecture given to colleagues in 1858, it is clear that Virchow understood that deep vein thrombosis and pulmonary embolism were part of the same condition, a condition which could result in sudden death or in spontaneous recovery (Virchow 1971):

> By no means rarely do these [peripheral veins] become quite filled with masses of coagulum. As long however as the thrombus is confined to the branch itself, so long the body is not exposed to any particular danger...Only the greater number of the thrombi in the small branches do not content themselves with advancing up to the level of the main trunk, but pretty constantly new masses of coagulum deposit themselves from the blood upon the end of the thrombus layer after layer, the thrombus is prolonged beyond the mouth of the branch into the trunk in the direction of the current of blood...It is these prolonged plugs that constitute the source of real danger; it is in them that ensues the crumbling away which leads to secondary occlusions in remote vessels...This gives rise to the very frequent process upon which I have bestowed the name of Embolia...Into the pulmonary artery the introduced fragments of thrombus of course penetrate to different depths according to their size...In the case of very large fragments even the principal trunks of the pulmonary artery are blocked up and instantaneous asphyxia ensues; other fragments again penetrate into the most minute arteries...it also happens that the secondary disturbances, like those at the spot whence the fragments were detached, run a very favourable course, the embolus like the thrombus becoming converted into pigment and connective tissue, and at the same time growing smaller.

Virchow also postulated that venous stasis, hypercoagulability, and damage to the vessel wall were predisposing factors for thrombosis (Virchow 1856). For more than a century these three mechanisms, referred to as "Virchow's triad", have provided a useful framework with which to consider the causes of venous thromboembolism. A limitation of this taxonomy, however, is that some risk factors fit into more than one category — for example, the increased risk of venous thromboembolism during pregnancy can be attributed both to a hormonally-induced hypercoagulable state and to venous stasis (Rosendaal et al. 2003a). An alternative approach in recent years has been

to classify risk factors according to whether they are inherited or acquired (Rosendaal 1999a).

While many acquired risk factors for venous thromboembolism have now been identified, two particular exposures — the use of combined oral contraceptives (that is, oral sex hormone preparations that contain both an oestrogen and progestogen component) and long-distance air travel — have generated considerable professional and public concern in recent years. The research which will be described in this thesis examined the relationships between these exposures and fatal pulmonary embolism. A postulated link between a third exposure — the use of psychotropic drugs — and death from pulmonary embolism was also explored. These risks were examined in three inter-related national population-based studies. Specifically, the research was based on all men and women aged 15 – 59 years, who died in New Zealand between 1990 and 2000, for whom the underlying cause of death was pulmonary embolism. This group included both men and women who were living in New Zealand at the time of their death, as well as people who happened to die while visiting the country (hereafter referred to as overseas visitors). A case-control study, restricted to those people who were normally resident in New Zealand, was undertaken to investigate the potential associations between fatal pulmonary embolism and the use of combined oral contraceptives and psychotropic drugs. Sex and age-matched controls were randomly selected from the general practices to which the cases had belonged. Information about drug exposures and other risk factors for venous thromboembolism was abstracted from the records of general practitioners, family planning clinics, and mental health services. A second case-control study, in which computer-assisted telephone interviews were undertaken with the next of kin of cases who were resident in New Zealand and with sex and age-matched controls randomly selected from the New Zealand electoral roll, explored the possible association between long-distance air travel and death from pulmonary embolism. A descriptive study based on official migration data and deaths in all recent air travellers (people resident in New Zealand and overseas visitors) was also undertaken to estimate the absolute risk of dying from pulmonary embolism following long-distance air travel.

Throughout this and subsequent chapters, combined oral contraceptives will be referred to simply as "oral contraceptives" or "the pill". Oral sex hormone contraceptive

products that contain a progestogen, but no oestrogen, will be referred to as progestogen-only pills.

1.2 OVERVIEW OF CHAPTERS

The thesis is divided into four parts. Part I, entitled *Overview*, comprises two chapters. This first chapter, as well as providing an overview of the thesis, briefly describes the epidemiology of venous thromboembolism, including the established risk factors for the condition. The diagnosis and treatment of deep vein thrombosis and pulmonary embolism are also outlined, since an understanding of the potential pitfalls in diagnosis is critical for later discussions about possible biases in epidemiological studies of venous thromboembolism. The second chapter discusses the methods used to identify the cases who were eligible for inclusion in the research presented in this thesis — that is, men and women aged 15 – 59 years who died in New Zealand between 1990 and 2000, for whom the underlying cause of death was pulmonary embolism.

Part II of the thesis, entitled *Fatal pulmonary embolism and the use of medicines*, consists of four chapters. The literature about venous thromboembolism and the use of oral contraceptives and of psychotropic drugs is reviewed in Chapter 3. In Chapter 4, the objectives and methods of the case-control study which explored the associations between fatal pulmonary embolism and the use of oral contraceptives and psychotropic drugs are outlined, as are the methods used to estimate the absolute risk of death from pulmonary embolism in users of oral contraceptives. The results of this research are presented in Chapter 5 and a discussion follows in Chapter 6.

Part III, *Fatal pulmonary embolism and long-distance air travel*, comprises five chapters. Chapter 7 reviews the evidence for an association between long-distance air travel and venous thromboembolism. Chapter 8 outlines the objectives and methods of the descriptive study of long-distance air travel and fatal pulmonary embolism. The results of this study are presented and discussed in Chapter 9. In Chapter 10, the objective and methods of the case-control study which examined the potential association between long-distance air travel and death from pulmonary embolism are provided. The results and discussion follow in Chapter 11.

Part IV, *Conclusion*, consists of the final chapter of the thesis in which the results of the research are summarised and the implications of the findings and research methods are discussed.

1.3 DIAGNOSIS AND TREATMENT OF VENOUS THROMBOEMBOLISM

1.3.1 Diagnosis

Although venous thrombosis can occur in any vein, the vast majority of venous thrombi arise in the veins of the lower limb. The classical symptoms and signs of deep vein thrombosis are pain, tenderness, swelling, distension of superficial veins, erythema, and increased warmth of the affected limb (Blann and Lip 2006). For pulmonary embolism, the characteristic symptoms and signs include dyspnoea, tachypnoea, pleuritic chest pain, cough, haemoptysis, tachycardia, and circulatory collapse. However, only about a quarter of people with suspected deep vein thrombosis actually have the condition and, conversely, some episodes of venous thrombosis are asymptomatic (Kyrle and Eichinger 2005). The same problem is encountered with pulmonary embolism. Indeed, it is thought that about 50 – 80% of people with symptomatic deep vein thrombosis have asymptomatic pulmonary embolism (Blann and Lip 2006). Hence, the diagnosis of venous thromboembolism based solely on symptoms and physical examination is unreliable and more objective investigations are required.

While contrast venography has been regarded as the gold standard method for the investigation and diagnosis of suspected deep vein thrombosis, it is an invasive procedure and in recent years non-invasive compression ultrasonography has become the preferred first-line imaging technique (Blann and Lip 2006). Ultrasonography has a high sensitivity and specificity for the diagnosis of proximal (above the knee) thrombosis, however it performs poorly in detecting deep vein thrombosis in the calves (Kyrle and Eichinger 2005).

The original gold standard test for pulmonary embolism, pulmonary angiography, has largely been replaced by less invasive investigations (Goldhaber 2004). Initially, a ventilation-perfusion lung scan was the preferred alternative test and a high probability scan was as useful as pulmonary angiography in making a diagnosis of pulmonary embolism. However, because many ventilation-perfusion scans are of intermediate or

indeterminate probability, contrast-enhanced computed tomography (CT) is increasingly the investigation of choice.

In recent years, the advent of methods for measuring the concentration of plasma D-dimer (a cross-linked fibrin derivative produced by endogenous fibrinolysis) have improved the diagnostic efficiency in people with suspected venous thromboembolism (Goldhaber 2004; Kyrle and Eichinger 2005). Diagnostic algorithms for deep vein thrombosis and pulmonary embolism, which include the assignment of clinical probability scores (based on medical history and physical examination), have been developed to guide the appropriate use of investigations (Blann and Lip 2006). For example, in people with a low pre-test probability score for deep vein thrombosis or pulmonary embolism, the initial investigation of choice is a D-dimer test. In such persons, a normal D-dimer concentration has a high negative predictive value and no further tests are indicated. If, however, the D-dimer concentration is higher than normal, further investigations (lower limb ultrasonography, ventilation-perfusion scan, or contrast-enhanced CT scan) are needed to confirm, or rule out, venous thromboembolism. This is because elevated D-dimer levels are found not only with venous thromboembolism, but also with myocardial infarction, pneumonia and other infections, cancer, pregnancy, and following surgery (Goldhaber 2004).

1.3.2 Treatment

The efficacy of intravenous heparin in reducing mortality in patients with pulmonary embolism was first established in the late 1930s (Hume 1963). A decade later, following the purification of an anticoagulant substance in spoiled sweet-clover hay, the first oral anticoagulant, bishydroxycoumarin, was successfully used to treat patients with venous thromboembolism. For many years, the standard approach to the treatment of deep vein thrombosis and pulmonary embolism was to administer unfractionated heparin intravenously to achieve rapid and ongoing anticoagulation until a concomitantly administered oral vitamin K antagonist, such as warfarin, took effect (Goldhaber 2004; Kyrle and Eichinger 2005). In recent years, intravenous heparin has increasingly been replaced by weight-adjusted doses of low-molecular weight heparins administered subcutaneously. In general, oral anticoagulation therapy is given for three to six months following a venous thromboembolic episode (Blann and Lip 2006). For certain people with ongoing risk factors or recurrent events, however, therapy is

continued indefinitely. More intensive treatment, such as fibrinolysis and embolectomy, is reserved for patients with massive pulmonary embolism and cardiogenic shock. Similarly, the use of inferior vena cava filters is confined to people with pulmonary embolism in whom the risk of bleeding with anticoagulation is high and in those who have developed recurrent pulmonary embolism during anticoagulation therapy.

1.4 DESCRIPTIVE EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM

1.4.1 Incidence

The annual incidence of venous thromboembolism in cohort studies in western countries such as the United States of America (USA) (Anderson et al. 1991; Silverstein et al. 1998; Tsai et al. 2002; Cushman et al. 2004), Sweden (Nordström et al. 1992; Hansson et al. 1997), France (Oger 2000), and the United Kingdom (UK) (Huerta et al. 2007) has been estimated to be about 1 – 2 per 1,000 persons. These figures represent the overall incidence in the populations which were studied — in fact, the frequency of venous thromboembolism increased markedly with increasing age in all of the quoted studies. In one population-based study in the USA, for instance, the annual incidence in men aged 15 – 29 years, 55 – 64 years, and $\geq$ 85 years was about 1 per 10,000, 1 per 1,000, and 1 per 100 respectively (Silverstein et al. 1998).

Data about the relationship between sex and the incidence of venous thromboembolism are conflicting. Some researchers have reported that women of child-bearing age have higher rates than men of the same age, a pattern which is reversed in older age groups (Silverstein et al. 1998; Oger 2000; Huerta et al. 2007). Conversely, other investigators have found that men have a slightly higher incidence at all ages (Anderson et al. 1991; Tsai et al. 2002; Cushman et al. 2004). Yet others have observed equal incidence in men and women (Nordström et al. 1992). The inconsistency in the results might be due to variations in exposure to exogenous risk factors by sex and age. In a recent meta-analysis, the risk of recurrent episodes of venous thromboembolism following cessation of treatment was found to be higher in men (McRae et al. 2006).

The incidence of venous thromboembolism has been shown to vary by ethnicity. For example, indigenous people in Alaska, and other states in the USA, have been found to

have lower rates of deep vein thrombosis and pulmonary embolism than people classified as white or African American (Stein et al. 2004a). Similarly, lower rates of venous thromboembolism have been reported for Hispanic Americans (White et al. 1998) and Americans of Asian or Pacific Island ethnicity (White et al. 1998; Stein et al. 2004b). While it is possible that these findings could be an artefact of differential access to health care and diagnostic facilities, the reported lower incidence of venous thromboembolism in Indigenous, Hispanic, Asian, and Pacific Island populations in the USA is consistent with an observation that the prevalence of one of the inherited thrombophilic mutations (factor V Leiden) is much lower in these groups than in Caucasian Americans (Ridker et al. 1997a). Other investigators have also reported a low prevalence, or indeed absence, of factor V Leiden in various populations in which venous thromboembolism is uncommon (Rees et al. 1995; Van de Water et al. 1997). A similar pattern has been observed with another inherited thrombophilic abnormality, prothrombin G20210A (Rosendaal et al. 1998). Such findings make it more probable that at least part of the observed differences in incidence by ethnicity is real and not due to referral and diagnostic biases.

It is likely that the published incidence figures are underestimates of the true frequency of venous thromboembolism in the populations which were studied. The reasons for this are two-fold. First, as Virchow described, episodes of deep vein thrombosis and pulmonary embolism may spontaneously resolve (Virchow 1971). Moreover, while some people with venous thromboembolism develop the classical symptoms of deep vein thrombosis or pulmonary embolism, many such events provoke only minor, or indeed, no symptoms and are therefore not identified (Goldhaber 2004; Kyrle and Eichinger 2005). Second, even if suspected events do come to the attention of medical professionals, as already noted, the diagnosis of venous thromboembolism on the basis of symptoms and physical examination alone is unreliable (Goldhaber 2004; Kyrle and Eichinger 2005). Hence, the probability that acute deep vein thrombosis or pulmonary embolism will be detected depends on the availability of diagnostic tests, whether the patient is referred for diagnostic assessment, and the sensitivity and specificity of the investigations which are performed. In the instance of fatal events, pulmonary embolism may go unrecognised if a necropsy is not performed because the death may be attributed to other causes of sudden death such as myocardial infarction and cardiac arrhythmia. Indeed, necropsy studies have suggested that the majority of pulmonary emboli which prove fatal are not diagnosed before death (Dalen 2002).

1.4.2 Major sequelae of venous thromboembolism

Fatal pulmonary embolism

As Virchow first observed, thrombus which forms in the deep veins of the legs sometimes propagates proximally into larger vessels and such thrombi may embolise to the lungs (Virchow 1971). If sufficiently large, pulmonary emboli may completely occlude the main pulmonary arteries and result in sudden death. Because many episodes of venous thromboembolism remain undetected there is some uncertainty about the figures, however it is thought that up to 20 – 25% of untreated thrombi in the deep veins of the calf propagate proximally into the upper leg and, of these, about half embolise to the lungs (Dalen 2002)).

Published estimates of the case-fatality rate for venous thromboembolism vary widely according to the source of the study group (population-based, hospital admissions, or clinical trial participants), the type of venous thromboembolic events studied (idiopathic or events associated with major co-morbidities), and the period of follow-up. Moreover in some studies, deaths from pulmonary embolism are not distinguished from mortality from any cause. For example, in a population-based study of 2,218 people with a first episode of deep vein thrombosis or pulmonary embolism in Olmsted County in the USA, the reported 30-day mortality rate was 28% (Heit et al. 1999). The study included people who developed venous thromboembolism following surgery, trauma, prolonged immobility, or in association with pregnancy, active cancer, and other serious illnesses. Hence, it is likely that some of the deaths were due to events other than pulmonary embolism and, moreover, that a proportion of deaths in which the mechanism of death was pulmonary embolism had other underlying causes. In an international study of 2,454 consecutive cases of pulmonary embolism in seven countries in Europe and North America, the three-month mortality rate was 17.4% for deaths from all causes and 7.9% for pulmonary embolism (Goldhaber et al. 1999). As in the previous study, many of the cases had major risk factors for venous thromboembolism. Similarly, 17% of 193 consecutive patients admitted to hospital in the Netherlands with pulmonary embolism died during the first six months after diagnosis (van Beek et al. 1997). Of these deaths, 5% were attributed to recurrent pulmonary embolism. A comparable in-hospital mortality rate (14.0%) was found in a Japanese study of 309 patients with pulmonary embolism, although it was not clear whether this included deaths from all causes (Nakamura et al. 2001). In another hospital-based study, in a defined geographical area

of the USA, the in-hospital case-fatality rate for 405 patients admitted with a first episode of deep vein thrombosis or pulmonary embolism was rather misleadingly quoted as 12%, however this figure included deaths from any cause (Anderson et al. 1991).

Lower estimates of case-fatality, ranging from 2.5 to 5.0% during the first 1 – 2 weeks following diagnosis, have been reported in trials of diagnostic methods (Carson et al. 1992) and treatment of pulmonary embolism (Simonneau et al. 1997; The Columbus Investigators 1997). These findings are not surprising, given the selected nature of trial participants and the fact that the study members survived long enough to enter the trial. Indeed, in a meta-analysis based on 25 prospective cohort studies and randomised controlled trials published between 1966 and 1997, the estimated case-fatality rates during a three-month period of anticoagulation were 0.4% (95% CI 0.2 – 0.6) for people initially diagnosed with deep vein thrombosis and 1.5% (95% CI 0.9 – 2.2) for those with pulmonary embolism (Douketis et al. 1998). However, higher rates were found for recurrent events; in patients who originally presented with deep vein thrombosis, 5.1% died after cessation of treatment for a recurrent episode. Of the patients with pulmonary embolism at baseline, 26.4% died during or after treatment of a subsequent venous thromboembolic event.

In a recent large population-based study of deep vein thrombosis and pulmonary embolism, the overall 28-day case-fatality rate was estimated to be 11% (Cushman et al. 2004). In an analysis stratified by patient characteristics, the case-fatality rates for idiopathic venous thromboembolism, events associated with major risk factors such as surgery and trauma (but not cancer), and cancer-related events were 5% (95% CI 1 – 9), 7% (95% CI 2 – 13), and 25% (95% CI 15 – 36%) respectively (Cushman et al. 2004). Differences in case-fatality rates by age and ethnicity have also been reported (Stein et al. 2004).

The most widely quoted case-fatality rate for venous thromboembolism is 1 – 2% (Rosendaal 1999a), although it is not entirely clear where this estimate originated. A figure closer to 5% for idiopathic venous thromboembolism seems more plausible based on the above data.

Chronic thromboembolic pulmonary hypertension

In a small proportion of people who survive a pulmonary embolic event, the vascular obstruction persists, leading to chronic pulmonary hypertension (Fedullo et al. 2001). Without pulmonary thromboendarterectomy, the condition progresses to right heart failure and eventual death. In a recent study, 4% of people with a first episode of pulmonary embolism developed chronic thromboembolic pulmonary hypertension during the first two years of follow-up (Pengo et al. 2004).

Post-thrombotic syndrome

Between 20 and 50% of people with symptomatic deep vein thrombosis develop a chronic condition known as the post-thrombotic syndrome within the first two years following diagnosis and treatment (Kahn and Ginsberg 2004). People with this condition typically suffer from chronic leg swelling, pain, and venous insufficiency which, in severe cases, can lead to skin ulceration. Thrombus-induced damage to the venous valves and subsequent venous hypertension is thought to be responsible. The condition has been found to have a considerable impact on quality of life (Kahn et al. 2002).

Recurrence of venous thromboembolism

As with case-fatality rates, the reported proportions of people with venous thromboembolism who suffer recurrent events varies according to the populations studied. In the meta-analysis referred to above, for instance, 3.8% of patients with deep vein thrombosis at baseline had a non-fatal recurrent episode of venous thromboembolism while being treated with anticoagulants (Douketis et al. 1998). Comparable rates of recurrence during treatment have been reported for pulmonary embolism (Nijkeuter et al. 2007). The annual likelihood of a recurrent episode of deep vein thrombosis following a first event is thought to be about 5 – 15%, with about 25% of patients having had a recurrence by four years (Kyrle and Eichinger 2005). In a recent study of people with a first episode of idiopathic pulmonary embolism, 17% developed a recurrent venous thromboembolic event during the first 30 months following cessation of anticoagulation (Eichinger et al. 2004). The risk of recurrence appears to be lower for people with post-operative venous thromboembolism (Goldhaber 2004; Kyrle and Eichinger 2005).

1.5 RISK FACTORS FOR VENOUS THROMBOEMBOLISM

Venous thromboembolism is a multi-causal disease — that is, the presence of more than one risk factor is usually required to trigger thrombosis (Rosendaal 1999a). Moreover, there is increasing recognition that inherited and acquired risk factors frequently interact so that the combined risks are greater than the sum of the individual risks. Thus, the importance of individual risk factors depends not only on their associated relative risks, but also on how commonly they occur, and whether they interact with other risk factors.

As will be seen in the following sections, although venous and arterial thrombosis share a few risk factors in common, many of the causes of venous thromboembolism differ from those of arterial cardiovascular disorders such as myocardial infarction and stroke (Tsai et al. 2002).

1.5.1 Inherited risk factors

Familial thrombophilia

In recent decades, several inherited abnormalities have been identified which increase the susceptibility of affected persons to venous thromboembolism. The first such familial thrombophilic defect to be described was a deficiency in the naturally occurring anticoagulant, antithrombin (Egeberg 1965). Some 20 years later, the thrombogenic effects of deficiencies in two other anticoagulants, protein C (Griffin et al. 1981) and protein S (Schwarz et al. 1984), were discovered. These deficiencies are rare, but strong, risk factors for venous thromboembolism (Rosendaal and Bovill 2002). Other rare inherited thrombophilias include dysfibrinogenaemia (Beck et al. 1965) and abnormal plasminogen (Aoki et al. 1978).

During the 1990s, considerable advances were made in the understanding of the aetiology of venous thromboembolism and the complex interactions between inherited and environmental risk factors. In 1993, resistance to activated protein C was demonstrated in several members of a family with a strong history of venous thrombosis (Dahlbäck et al. 1993). Subsequently it was determined that a single point mutation in coagulation factor V, the so-called factor V Leiden mutation, caused activated protein C resistance (Bertina et al. 1994). Intriguingly, it later emerged that among carriers of factor V Leiden, the relative risk of pulmonary embolism was about half that of deep vein thrombosis (Bounameaux 2000). Inherited activated protein C resistance was also

shown to occur in the absence of factor V Leiden and acquired resistance was demonstrated in users of oral contraceptives and hormone replacement therapy (Rosendaal 1999b). In 1996, a second variant coagulation factor, prothrombin G20210A, was identified (Poort et al. 1996). Carriers of this mutation were shown to have elevated concentrations of prothrombin and an increased risk of venous thromboembolism. High levels of prothrombin in people without the mutation were also shown to predispose to venous thrombosis. Although factor V Leiden and prothrombin G20210A occur reasonably commonly in populations of European ethnicity (Rosendaal and Bovill 2002), the majority of carriers do not develop thrombosis (Ridker et al. 1997b; Bank et al. 2004).

Interactions have been demonstrated between familial thrombophilias and acquired risk factors. For example, the risk of venous thromboembolism during oral contraceptive use or pregnancy is much higher for women with deficiencies of antithrombin, protein C, or protein S, and for carriers of factor V Leiden or prothrombin G20210A, than it is for women without such abnormalities (Rosendaal 1999a; Rosendaal et al. 2003a).

1.5.2 Acquired risk factors

Previous venous thromboembolism

As already discussed in an earlier section, a considerable proportion of people who have had one venous thromboembolic episode will subsequently develop further events. Damage to the venous valves and resultant stasis is thought to contribute to the increased risk of deep vein thrombosis in people with previous events (Rosendaal et al. 2003a). Thrombosis and inflammation in the superficial veins of the leg, also appear to increase the risk of developing deep vein thrombosis (Kyrle and Eichinger 2005). Varicose veins are generally considered to be a risk factor for venous thromboembolism (Goldhaber 2004; Kyrle and Eichinger 2005), although there is some evidence to suggest that the risk is only increased in younger age groups (Heit 2003).

Age

The risk of venous thromboembolism escalates with advancing age (Goldhaber 2004; Kyrle and Eichinger 2005). Hence, the attributable risk of an exposure associated with, for example, a two-fold increased risk of venous thromboembolism will rise markedly with increasing age. Because of the complex interactions between age and other risk

factors, the likelihood that exposure to a particular set of risk factors will trigger thrombosis is lower in younger people than in older people (Rosendaal 1999a).

Malignancy

A link between malignancy and venous thromboembolism was first described in 1865 (Lip et al. 2002). Not only is the risk of venous thromboembolism increased in people with diagnosed active cancer, but apparently idiopathic venous thromboembolism is sometimes the presenting symptom of an occult malignancy, especially of the liver, pancreas, ovary, and brain (Kyrle and Eichinger 2005). Similarly, the presenting symptom of occult cancer may be recurrent thrombosis during anticoagulant treatment (Goldhaber 2004). Indeed, the risk of discovering a malignancy is increased for at least two years following an episode of pulmonary embolism; the prognosis of such cancers is generally poor.

Acute and chronic medical conditions

An increased risk of venous thromboembolism has been associated with current or repeated hospital admissions, as well as residence in chronic care facilities (Goldhaber 2004; Kyrle and Eichinger 2005). More specifically, several acute medical conditions — including myocardial infarction, respiratory failure, and infection — have been shown to increase the risk (Kyrle and Eichinger 2005). The presence of antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies) increases the risk of venous thromboembolism in people with systemic lupus erythematosus and other autoimmune diseases, as well as people without these conditions (Goldhaber 2004; Kyrle and Eichinger 2005). Chronic conditions associated with an elevated risk include limb paresis, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, and congestive heart failure (Goldhaber 2004; Kyrle and Eichinger 2005).

Other conditions which are thought by some commentators to predispose to venous thromboembolism include diabetes (Goldhaber 2004), nephrotic syndrome (Kyrle and Eichinger 2005), myeloproliferative disorders such as polycythaemia rubra vera and essential thrombocythaemia (Kyrle and Eichinger 2005), chronic obstructive pulmonary disease (Goldhaber 2004), and hypertension (Goldhaber 2004). Rarer conditions include thrombotic thrombocytopenic purpura (Heit 2003), thromboangiitis obliterans (Heit 2003), paroxysmal nocturnal haemoglobinuria (Kyrle and Eichinger 2005),

congenital venous malformations (Kyrle and Eichinger 2005), and Behcet's syndrome (Kyrle and Eichinger 2005). Certain behaviours, such as intravenous drug use (Kyrle and Eichinger 2005), increase the risk, as does invasive medical equipment such as central venous catheters (Goldhaber 2004), permanent pacemakers (Goldhaber 2004), internal cardiac defibrillators (Goldhaber 2004), and vena cava filters (Kyrle and Eichinger 2005). It has been suggested that dehydration increases the risk of venous thromboembolism (Mammen 1992), although there is a surprising lack of evidence from epidemiological studies to support this belief.

Obesity is commonly accepted as a risk factor for deep vein thrombosis and pulmonary embolism (Goldhaber 2004; Kyrle and Eichinger 2005). A dose-response of increasing risk of venous thromboembolism with increasing body mass index (BMI) has been found in large prospective studies (Goldhaber et al. 1997; Huerta et al. 2007).

Medicines

Apart from oral contraceptives and psychotropic drugs, which are discussed in Chapter 3, several medicines have been associated with an increased risk of venous thromboembolism. Oral hormone replacement therapy has been confirmed as a risk factor in randomised controlled trials (Beral et al. 2002). Elevated risks have also been reported for exogenous oestrogens used in other contexts, such as for the treatment of prostate cancer (Anderson and Spencer 2003). It seems, however, that oestrogen administered transdermally is not a risk factor (Scarabin et al. 2003).

Oral and injectable progestogen-only contraceptives and combined injectable contraceptives do not appear to be associated with venous thromboembolism (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1998; Heinemann et al. 1999; Vasilakis et al. 1999a). However, an increased risk of venous thrombosis has been observed with higher doses of unspecified progestogens administered orally for therapeutic indications such as the treatment of menorrhagia and dysfunctional vaginal bleeding (Poulter et al. 1999a; Vasilakis et al. 1999a). Hormones used during in-vitro fertilisation treatment and ovulation induction have also been implicated (Bloemenkamp 2005).

The selective oestrogen-receptor modulator, raloxifene, and oestrogen agonist-antagonist, tamoxifen, which are used to treat or prevent breast cancer have both been

shown in randomised controlled trials to increase the risk of venous thromboembolism (Goldhaber 2004; Kyrle and Eichinger 2005). Similarly, increased risks have been observed with thalidomide, various chemotherapy agents and heparin-induced thrombocytopenia (Kyrle and Eichinger 2005).

Other transient or removable risk factors

Several other transient risk factors for venous thromboembolism have been identified, including pregnancy and the puerperium, immobility and prolonged bed rest, and major trauma, especially spinal injuries and pelvic or leg fractures (Goldhaber 2004; Kyrle and Eichinger 2005). Major surgery, in general, also increases the risk of venous thromboembolism. However, the risk is particularly high for orthopaedic surgery of the lower limb (especially total hip and knee joint replacements and hip fracture surgery), abdominal and pelvic surgery, neurosurgery (especially craniotomy for brain tumours), and vascular surgery (Goldhaber 2004; Kyrle and Eichinger 2005). The likelihood of post-operative venous thromboembolism is increased by the presence of other risk factors, particularly cancer (Kyrle and Eichinger 2005). Evidence about smoking as a risk factor is equivocal; some reviewers have interpreted the data as indicating an increased risk (Goldhaber 2004) while others have not (Heit 2003).

1.5.3 Risk factors which may be inherited or acquired

Several risk factors for venous thromboembolism appear to have mixed genetic and environmental, or uncertain, origins. These include high concentrations of several clotting factors such as factors VIII (Koster et al. 1995), IX (van Hylckama Vlieg et al. 2000), and XI (Meijers et al. 2000a), as well as high levels of thrombin activatable fibrinolysis inhibitor (van Tilburg et al. 2000). Homocysteinaemia, a risk factor for both venous and arterial thrombosis, may be due to mutations of cystathionine β-synthase and methylene tetrahydrofolate reductase or to an inadequate intake of folic acid, vitamin B6, or vitamin B12 (Rosendaal 1999a). It is uncertain whether increased levels of lipoprotein(a), which predispose to venous thromboembolism, are due to inherited or acquired factors (Goldhaber 2004).

CHAPTER 2 IDENTIFICATION OF MEN AND WOMEN WHO DIED FROM PULMONARY EMBOLISM IN NEW ZEALAND BETWEEN 1990 AND 2000

2.1 INTRODUCTION

This chapter describes the methods used to identify eligible cases for the research that will be discussed in Parts II (the case-control study of oral contraceptives and psychotropic drugs) and III (the descriptive and case-control studies of long-distance air travel) of this thesis. As will be explained in later chapters, ethical approval was granted by the regional ethics committees to examine existing death, hospital, general practice, and family planning clinic records for each case.

2.2 ASCERTAINMENT OF POTENTIAL CASES

2.2.1 Inclusion and exclusion criteria

The persons considered eligible for the research included all men and women aged 15 – 59 years, who died in New Zealand between January 1990 and December 2000, for whom the "underlying cause of death" was coded to one of the following rubrics of the ninth (deaths between 1990 and 1999) or tenth (deaths during 2000) revisions of the International Classification of Diseases: 415.1 (pulmonary embolism and infarction), 451 (phlebitis and thrombophlebitis), 453 (other venous embolism and thrombosis), I26.9 (pulmonary embolism without mention of acute cor pulmonale), I80 (phlebitis and thrombophlebitis), or I82 (other venous thromboembolism and thrombosis).

As will be explained in section 2.2.2, the "underlying cause of death" is supposed to be the factor that begins the sequence of events that leads to death. Deaths from pulmonary embolism that occurred post-operatively or in people with advanced cancer, for example, should not (if they were coded correctly) have been identified using the above rubrics. Hence, such deaths were excluded from the present research. Fatal pulmonary embolism which occurred as a complication of pregnancy, childbirth, or the puerperium was also excluded, as such events are coded to different rubrics from those listed above.

Potential cases were excluded if they were found to have insufficient clinical or pathological evidence for a diagnosis of pulmonary embolism. Thus, people for whom the underlying cause was coded as 451 or 453 (ninth revision) or I80 or I82 (tenth revision) were included in the present research only if there was clear evidence that distal venous thrombosis had been complicated by pulmonary embolism.

It was originally hoped to include people who died before 1990, but a pilot study involving women aged 15 – 49 years showed that it was not feasible to include such deaths because many medical records had been destroyed or lost. For example, general practice records were located for just seven of the 18 women who died between 1986 and 1989, and hospital records were found for only three of the nine women who had died in hospital.

2.2.2 The management of mortality data in New Zealand

Following most deaths in New Zealand, the doctor who attended the patient during their final illness completes a Medical Certificate of Causes of Death (New Zealand Health Information Service 2001). This certificate, which was designed in accordance with the International Death Certificate advocated by the World Health Organization (WHO), allows for the entry of the direct and antecedent causes of death, as well as other conditions that are considered to have contributed to the death. The direct cause of death is defined as the disease, injury or complication directly leading to death, while the antecedent causes are those morbid conditions (if any) that gave rise to the direct cause. The underlying condition should be recorded last in this causal sequence.

The Coroners Act 1988 (and the subsequent Coroners Act of 2006) requires that certain deaths are referred to a coroner for certification of cause (New Zealand Health Information Service 2001). These include deaths without known cause; suicides; deaths resulting from unnatural or violent causes; deaths where a doctor has not issued a death certificate; deaths that occurred during or as a result of a medical, surgical or dental procedure, or an anaesthetic; and deaths of persons detained by the police or certain institutions. If a natural cause of death is established after preliminary investigations, the coroner is permitted to certify the cause of death without holding a formal inquest (except in certain situations, such as a death in police custody, in which an inquest is mandatory). To ensure that deaths are classified consistently, coroners are required to

record the sequence of morbid events in the same manner as doctors completing the Medical Certificate of Causes of Death.

For each death, a copy of the Medical Certificate of Causes of Death or the coroner's report is sent to the Registrar-General of Births, Deaths, and Marriages, who is responsible for keeping a register of the causes of death (New Zealand Health Information Service 2001). This information is then forwarded to the New Zealand Health Information Service in the Ministry of Health, where the underlying cause of death is classified according to the International Classification of Diseases. For some deaths, information from necropsy reports sent by hospitals and private pathologists is also used to assign the underlying cause of death.

2.2.3 Identification of potential cases

For the present research, the New Zealand Health Information Service was asked to identify all people who met the eligibility criteria and to provide the following information about each person: the National Health Index (NHI) number, full name, sex, date of birth, date of death, prioritised ethnicity (see Chapter 10), the underlying cause of death, other contributing causes, death registration year, death registration number, whether a necropsy was performed, and whether the death was certified by a doctor or a coroner.

There were 149 people (53 men and 96 women) who met the eligibility criteria: 140 had been usually resident in New Zealand at the time of death and nine were overseas visitors. The underlying cause of death was certified by a coroner in 123 cases and by a doctor in 26. Ten of the coroner-certified deaths had been the subject of an inquest. A necropsy was performed on 132 (89%) of the potential cases.

2.3 REVIEW OF EXISTING SOURCES OF INFORMATION ABOUT POTENTIAL CASES

2.3.1 Phases of data collection

The present research involved three phases of data collection. In the first, information about women aged 15 – 49 years was obtained for a case-control study of oral

contraceptive use and fatal pulmonary embolism. Because of the delays inherent in coding mortality data, at the time the study was initiated it was possible to include only those deaths that had occurred before August 1998.

The case-control study was later expanded in order to examine the association between psychotropic drugs and fatal pulmonary embolism in men and women aged 15 – 59 years who died between January 1990 and December 1998. Hence, in the second phase of data collection, information was sought about men aged 15 – 59 years and women aged 50 – 59 years who died between January 1990 and December 1998, as well as women aged 15 – 49 years who died in the final months of 1998. The full methods and results of the case-control study of the use of oral contraceptives and psychotropic drugs are presented in Chapters 4 and 5.

During the third and final phase of data collection, the case series was extended to include men and women aged 15 – 59 years who died in 1999 and 2000. The descriptive and case-control studies of long-distance air travel and fatal pulmonary embolism, which are discussed in Chapters 8 – 11, were based on this extended series of men and women aged 15 – 59 years who died between 1990 and 2000.

2.3.2 Death records

Coroner-certified deaths

The Department for Courts in Wellington was the central repository in New Zealand for coronial files during the three phases of data collection. To view the files of the 123 potential cases whose underlying cause of death was certified by a coroner, contact was made on three occasions with the Coronial Services Officer in Wellington. These approaches were followed by a visit by me or a research assistant to photocopy the records. All of the relevant files were located. Each file contained a statement by the coroner about the underlying cause of death, except for two deaths about which a coroner had yet to rule. Various other forms and reports were found in some, but not all, of the files. These included a Certificate as to Extinction of Life, a Statement of Identification form, a Notification of Death for Registration form, a report prepared by the Police for the coroner (the Police 47 form), a copy of the necropsy report, and further information from the Inquest if one had been held.

Unfortunately, only 56 of the 123 files contained a Police 47 form. During the study period, the police were required to complete this form for all deaths that were the subject of a coroner's inquiry. The form was used to record demographic data and next of kin details, as well as a description of the circumstances of death. Hence, it was a particularly valuable source of information about people who had died suddenly in the community. In addition, it often identified the general practitioner.

Since it was apparent that the Police 47 form was missing from the files of all the people who had died in one large centre, a telephone call was made to the mortuary in that city to ascertain whether copies of the forms were held locally. It transpired that it was indeed the practice in this centre, and in several others, to keep copies of the Police 47 form in the pathology department. Therefore, for all potential cases for whom the Police 47 was missing, a letter was sent to the pathologist who had conducted the necropsy to request a copy of the form (Appendix A, letters 1 – 3). When pathologists were unable to provide the forms, inquest officers at the local police stations were telephoned. A letter was sent to a coroner who was still reviewing one woman's death and he provided a copy of the Police 47 (Appendix A, letter 4). As can been seen in Table 2.1, most of the missing Police 47 forms were obtained using these approaches.

Necropsy reports were also missing from the files of six people and these were obtained from pathologists (*n=3*), hospital records (*n=2*), and the police (*n=1*).

Table 2.1 Acquisition of Police 47 forms, New Zealand residents and overseas visitors

Police 47 forms	Number of coroner-certified deaths
Obtained	
Source of Police 47 form	
Coroner's file held in the Department for Courts	56
Pathologist	52
Police inquest officer	7
Coroner	1
Total obtained	116
Not obtained	
Reasons why Police 47 form not obtained	
Police and pathologist's copies destroyed	3
Not sought because had extensive inquest records	1
Coroner did not become involved immediately after death so a Police 47 form was not completed	1
Not sought because excluded at outset of study	2
Total not obtained	7
Total number of coroner-certified deaths	**123**

Doctor-certified deaths

Copies of the Medical Certificate of Causes of Death for deaths that occurred in the earlier years of the study period were provided by the New Zealand Health Information Service. Certificates for later deaths were obtained from the Registrar-General of Births, Deaths, and Marriages. A necropsy had been performed after 11 of the 26 doctor-certified deaths. For six people, a copy of the necropsy report was provided along with the Medical Certificate of Causes of Death and for the remaining five, a copy was obtained from their hospital records.

Exclusion of deaths at the outset of the research

After examining the death records of six potential cases it was immediately apparent that the underlying cause of death was not pulmonary embolism. For three of these deaths, a necropsy revealed the underlying cause to be bilateral renal vein thrombosis in one, cerebral infarction in another, and pulmonary veno-occlusive disease in the third. A necropsy undertaken on the fourth person could find no obvious cause of death. The underlying causes in the remaining two persons were certified by their doctors as chronic renal failure and the Budd-Chiari Syndrome. These six people, who were all New Zealand residents, were therefore excluded. This left 143 potential cases (134 New Zealand residents and nine overseas visitors) for whom further information was sought.

2.3.3 Hospital records

Potential cases who died in hospital were identified using the death records described above. Admissions at any other time during the year before death were also ascertained from the National Minimum Dataset. For each admission, a letter was sent to the Senior Medical Advisor at the relevant hospital to seek permission for me to visit and view the records of that patient. The names and contact details of these doctors were provided by the Safety and Regulation Branch of the Ministry of Health. One of two standard letters was sent depending on whether the potential case had died in hospital or whether they had simply been admitted at some other time during the year before death (Appendix A, letters 5 – 10). In addition to seeking permission to examine the notes, the letter provided information about the study and requested that a copy of the front sheet relating to the most recent admission be sent in a reply-paid envelope. The front sheet

was sought so that any general practitioners who had not been named in death records could be identified before I visited the region in which the case had lived.

About two weeks after a letter had been sent to a Senior Medical Advisor, he or she was contacted by telephone and arrangements were made to view the records. Protracted negotiations with the Chief Executive at one hospital were required before permission was granted to examine hospital records, while another centre would not provide copies of the front sheet, but would allow the records to be viewed in person. In total, 27 hospitals around New Zealand were visited.

Of the 134 New Zealand residents, five were pronounced dead on arrival in hospital emergency departments although no records about these events were found at any of the hospitals. As can been seen in Table 2.2, two of the five had been admitted to the same hospital in the year before death. Another 55 New Zealand residents died in hospital, 31 of whom had also been admitted to the same or different hospitals at some other time during the year before death. The remaining 74 New Zealand residents did not die in hospital, although 19 were admitted to at least one hospital during the year before their death. The hospital records of all but three patients were examined: two had died in emergency departments and the records had been destroyed, and one other had undergone surgery in an unidentified hospital. It was concluded that this operation must have taken place in a private hospital as the admission was not recorded in the National Minimum Dataset (during the study period, discharges from private hospitals were inconsistently recorded in this database).

Of the nine overseas visitors, five died in hospital, one died on hospital premises while visiting a relative, and three died elsewhere (Table 2.3). The notes describing these events were all located and reviewed.

Table 2.2 Admissions to New Zealand hospitals, New Zealand residents not excluded at the outset

Admissions	Number of deaths (n=134)	Number for whom the records were located
Dead on arrival at hospital, not noted in hospital records (n=5)		
Admitted to same hospital at least once during year before death	2	2
Not admitted to any hospitals during year before death	3	-
Died in hospital (n=55)		
Admitted to same hospital at least once during year before death	19	19
Admitted to another hospital at least once during year before death	12	12
Not admitted to any hospitals during year before death	24	22*
Did not die in hospital (n=74)		
Admitted to one hospital at least once during year before death	15	14†
Admitted to two different hospitals during year before death	4	4
Not admitted to any hospitals during year before death	55	-

* Records for two cases who died in the emergency department were not found.
† Records for one case who had surgery in a private hospital were not found.

Table 2.3 Admissions to New Zealand hospitals, overseas visitors not excluded at the outset

Place of death	Number of deaths (n=9)	Number for whom the records were located
Died in hospital	5	5
Died while visiting a relative in hospital	1	1
Did not die in hospital	3	-

The information sought from the hospital records included the following, if available: the circumstances of the fatal episode, reported symptoms, and the results of any physical examination and diagnostic tests; the diagnosis and clinical course of any other events for which the person was hospitalised in the year before death; details of any previous illnesses (especially venous thromboembolism, cardiovascular disease, and diabetes); any major injury, surgery, prolonged immobility, or pregnancies in the year before death; contraceptive history; other medications used in the year before death; parity; smoking habits; ethnicity; weight; height; and any family history of venous thromboembolism. All data were abstracted from the notes and recorded using a unique study identification number.

2.3.4 General practice records

During the study period, there was no requirement for people living in New Zealand to formally register with a general practitioner and hence there was no centralised system which could be used to reveal the name of a patient's doctor. This meant that several methods had to be employed to identify the general practitioners of the 134 potential cases who were New Zealand residents. For 125 people, existing documents such as coroners' files (*n=71*), the Medical Certificate of Causes of Death (*n=1*), hospital records (*n=50*), the Centre for Adverse Reactions Monitoring files (*n=2*), and family planning clinic records (*n=1*), led to the general practitioner who was likely to hold the records of the potential case (Table 2.4). Sometimes this doctor was identified through a third party. For example, for three cases, letters were sent to the locum or on-call general practitioner who was named in the coroner's or hospital records and this doctor provided the name of the usual general practitioner (Appendix A, letters 11 and 12). Two potential cases, for whom the course of the fatal episode was rather protracted, had seen new doctors after the onset of their symptoms and these doctors identified the general practitioners whom the cases had attended before they became unwell. Several practices had also been sold, sometimes more than once, since the death of the potential case — although fortunately most continued to operate from the same premises and a telephone call to the practice was all that was required to establish the name of the doctor who had taken over. A further two practices had closed down, but the former general practitioners were traced using the electoral roll. One practice had been put into receivership after fraud investigations were initiated and the general practitioner to whom the practice had been sold suddenly left the country. It was established that many

patients had collected their records from the receivers and had joined one or other of the two remaining practices in the town, although some unclaimed files were still being held by the receivers because the district health board and other local health services had declined to take responsibility for them.

Various other methods were used to try and identify the remaining general practitioners, including writing to next of kin (Appendix A, letters 13 and 14) and ringing general practices in the towns in which the potential cases had lived. There were only two people for whom a general practitioner could not be identified. In addition to the above methods, the local police, coroners, pharmacies, private and hospital laboratories, and Independent Practitioner Associations were contacted. Unfortunately, because these two deaths occurred in 1992 and 1993, none of these organisations had reliable computer records for the relevant periods and the general practitioners remained unidentified.

Table 2.4 Sources of information used to identify general practitioners of New Zealand residents not excluded at the outset

Identification of general practitioners	Number of deaths (n=134)
Identified using existing records (n=125)	
1. Coroners' records identified:	
General practitioner	60
General practice attended by potential case	1
Doctor who confirmed death, was the partner of the usual general practitioner, but practice had subsequently been sold	1
Locum of another general practitioner in same town, that doctor identified the usual general practitioner	1
General practitioner on index date*, but practice had subsequently been sold	6
General practitioner on index date, but practice had subsequently been closed	2
2. Death certificate identified:	
General practitioner who saw potential case after the index date, that doctor identified the general practitioner on the index date	1
3. Hospital records identified:	
General practitioner	39
General practitioner who saw potential case after the index date, that doctor identified the general practitioner on the index date	1
Locum of usual general practitioner	1
General practitioner on index date, but practice had subsequently been sold	8
General practitioner on index date, but practice had subsequently been put into receivership	1
4. Centre for Adverse Reactions Monitoring records	2
5. Family planning clinic records	1
Identified using other methods (n=7)	
1. Phoned general practices in town in which case had lived	2
2. Identified incidentally when visiting general practice to view records of another case	1
3. Wrote to next of kin	4
General practitioner not identified (n=2)	2

* The date of onset of the fatal episode was taken as the index date.

Once the names of the 132 identified general practitioners or their replacements had been confirmed, they were sent a letter which outlined the aims of the research and requested permission to visit the practice to examine the records of the potential case (Appendix A, letters 15 – 17). As will be explained in Chapter 4, permission was also sought from the doctors of potential cases who died between 1990 and 1998 to view the records of four randomly selected controls. About a week after the letter had been sent, the general practitioner was telephoned to provide further information about the study and to arrange a suitable time for a visit.

None of the general practitioners refused to allow me to visit their practice, although four said that the files of the potential case had been destroyed at an earlier date and a further three reported that they could not find the records. The records of an eighth patient could not be found by the general practitioner, but a copy of the file was obtained from the coroner. This person was later determined to be ineligible for inclusion in the study. The records of two cases who died after 1998, and who were therefore not included in the case-control study of oral contraceptives and psychotropic drugs, were couriered to the Department of Preventive and Social Medicine by their general practitioners, one of whom had closed her practice. Thus, 122 visits were made to general practices throughout New Zealand. The files of 108 patients were found during these visits, often after quite some effort. For example, the records of the man who had belonged to the practice that was put into receivership were eventually found inside his family file at one of the other practices in town after a morning had been spent in the receiver's storage shed in a city about an hour away. Table 2.5 provides demographic and other information about the 21 men and women for whom general practitioner records were not found.

Table 2.5 New Zealand residents not excluded at the outset for whom general practitioner records could not be found

Year of death	Sex	Age (years)	Confirmation of diagnosis	Died in hospital	Other admission(s)*	Hospital records examined	Determined to be eligible	Comments
1990	Male	19	Necropsy	No	No	-	Yes	General practitioner had recently retired and sold practice. Visited practice and searched for records at practice and in off-site storage facility.
1990	Male	47	Necropsy	Yes	Yes	Yes	Yes	General practitioner had destroyed records.
1990	Male	50	Necropsy	No	No	-	Yes	General practitioner had destroyed records.
1990	Male	52	Nil	No	No	-	No	General practitioner could not find records.
1990	Male	53	Nil	Yes	Yes	Yes	No	Visited practice, found paper records of visits up until 1987 when switched to electronic records. Shifted premises several years after patient died. Computer records deleted.
1990	Male	54	Necropsy	Yes	No	Destroyed	Yes	General practitioner had retired and destroyed records.
1990	Male	55	Necropsy	Yes	No	Yes	Yes	Visited practice and searched for records. Found results of blood tests only.
1990	Male	58	Nil	No	Yes	Yes	No	Changed general practitioners on index date†, viewed these records. Visited former practice and searched for records.
1991	Female	28	Necropsy	No	No	-	Yes	General practitioner who was identified in coroner's records did not remember case and could not find records, thought he must have seen her when on call. Another general practitioner, who was identified in hospital records in 1990 and had retired in 1994, he searched through the files stored at his home.

Year of death	Sex	Age (years)	Confirmation of diagnosis	Died in hospital	Other admission(s)*	Hospital records examined	Determined to be eligible	Comments
1991	Female	30	Necropsy	Yes	Yes	Yes	Yes	General practitioner had destroyed records.
1991	Female	45	Necropsy	Yes	No	Yes	Yes	General practitioner had sold practice. Neither he, nor new general practitioner, was able to find records.
1991	Male	55	Necropsy	No	Yes	Yes	Yes	Visited practice and searched for records.
1993	Male	57	Necropsy	Yes	Yes	Yes	Yes	Visited practice, found paper records of visits up until 1991, also electronic files archived on defunct 5½ inch floppy disks. With the assistance of the doctor who developed the computer programme previously used by the general practitioner, the disks opened were by a biostatistician (Mr Peter Herbison) on an old computer in the Department of Preventive and Social Medicine. These contained records for 1992 only.
1995	Female	24	Necropsy	Yes	Yes	Yes	Yes	Visited practice and searched for records.
1996	Female	35	Necropsy	No	No	-	Yes	Visited practice and searched for records.
1997	Female	32	Necropsy	No	No	-	Yes	Visited practice and searched for records. Found a copy of a clinical summary which was sent to the coroner.
1997	Female	44	Necropsy	No	No	-	Yes	Visited practice and searched for records. Found records of visits up until 1989.
1997	Female	58	History reviewed by specialists in internal medicine‡	Yes	No	Yes	Yes	General practitioner had sold practice which was subsequently relocated to new premises. Visited practice and searched for records, general practitioner also searched through the files stored at his home.

Year of death	Sex	Age (years)	Confirmation of diagnosis	Died in hospital	Other admission(s)*	Hospital records examined	Determined to be eligible	Comments
1998	Male	50	Nil	No	Yes	Yes	No	Electronic records accidentally deleted by general practitioner's receptionist. Visited practice with doctor who developed the computer programme used by the general practitioner but he was unable to retrieve the records. Paper records also lost.
1999	Female	30	Necropsy	Yes	No	Yes	Yes	Visited practice, but general practitioner was unable to locate records.
2000	Female	41	Necropsy	Yes	No	Yes	Yes	Visited practice, but general practitioner was unable to locate records.

* Admission to hospital at any other time in year before death.
† The date of onset of the fatal episode was taken as the index date.
‡ Using standard criteria (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995a).

A standardised data form was used to record medical information abstracted from the medical records of each of the potential cases (Appendix B). Study identification numbers, rather than names, were recorded on these forms. Everything within a file was examined, including hospital and specialist letters, laboratory and radiology reports, as well as old notes that had been transferred from other practices. In the practices that maintained a dual records system, the electronic and paper records were both examined. The information that was sought will be described in more detail in Chapter 4.

2.3.5 Family planning clinic records

One of the aims of the present research was to examine the association between the use of medicines and fatal pulmonary embolism. Because many women obtain oral contraceptives or hormone replacement therapy from family planning clinics, it was decided to seek permission from the New Zealand Family Planning Association to examine any family planning clinic records that existed for the female cases (and their controls). More details will be provided in Chapter 4 about how such records were found, but what follows is a brief description of how the organisation came to participate in the study.

First, a letter was sent to the spokesperson for the Family Planning Association and the manager of professional medical services in the northern region (Appendix A, letter 18). The matter was then discussed at a national level by the Association's regional directors. In one region there was concern about allowing access to clinical data because patients are given an undertaking that information will not be provided to third parties. However, because patients are informed that Government agencies may request statistical information, the directors felt that the Association would be able to participate in the research if they were to receive a request from the Ministry of Health to do so. One of my supervisors, Professor Charlotte Paul, therefore contacted Dr Stewart Jessamine (Senior Medical Advisor in the Safety and Regulation Branch of the Ministry of Health), who then wrote to the Executive Director of the Family Planning Association to ask her to allow access to any relevant data. Following this, I was granted permission to view any records that existed for the female cases and controls. All information that was abstracted from the records was recorded on a form identical to that used during the general practice visits.

In several small towns where there were no Family Planning Association clinics, contraceptive clinics were run by hospitals or other organisations. Permission to view records was sought individually from these clinics.

2.3.6 Centre for Adverse Reactions Monitoring records

The Centre for Adverse Reactions Monitoring, a unit within the Department of Preventive and Social Medicine, receives spontaneous reports of adverse reactions to drugs from doctors and other health professionals throughout New Zealand. During the study period, several deaths from pulmonary embolism in women who were taking combined oral contraceptives were reported to the Centre. These reports, which were examined with the permission of the director, will be discussed in Chapter 5.

2.4 ELIGIBLE CASES AND EXCLUSIONS

2.4.1 Exclusions

Of the 149 potential cases originally identified by the New Zealand Health Information Service, a total of 28 were excluded for the reasons outlined in Table 2.6. Four people who did not have a necropsy were excluded after two specialists in internal medicine (a cardiologist and a respiratory physician) independently reviewed their presenting symptoms, signs, and the results of diagnostic tests. None of the four met standard diagnostic criteria for a probable or definite diagnosis of pulmonary embolism (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995a).

Table 2.6 Potential cases identified by the New Zealand Health Information Service who were excluded from the research, New Zealand residents and overseas visitors

Year of death	Sex	Age (years)	Who certified cause of death	Necropsy performed	Died in hospital	Other admission(s)*	Hospital records examined	GP records examined	Underlying cause of death
1990	Male	52	Coroner	Yes	No	No	-	Lost	PE found at necropsy, but underlying cause metastatic bowel cancer.
1990	Male	53	Doctor	No	No	Yes	Yes	Only up until 3 years before death	Metastatic bowel cancer.
1990	Male	58	Coroner	Yes	No	Yes	Yes	Records after index date only†	PE found at necropsy, but underlying cause high grade astrocytoma.
1990	Female	59	Doctor	No	Yes	Yes	Yes	Yes	Discussed with two specialists in internal medicine, insufficient evidence for diagnosis of PE.
1990	Male	59	Doctor	Yes	Yes	Yes	Yes	Yes	PE found at necropsy, but underlying cause chronic lymphocytic leukaemia.
1991	Female	44	Doctor	No	Yes	No	Yes	Yes	Discussed with two specialists in internal medicine, insufficient evidence for diagnosis of PE.
1991	Female	51	Coroner	Yes	No	Yes	Hospital not identified	Yes	PE found at necropsy, but left-sided total hip joint replacement (osteoarthritis) 14 days before onset of symptoms.
1991	Female	58	Coroner	Yes	Yes	Yes	Yes	Yes	PE found at necropsy, but hysterectomy (carcinoma-in-situ) and anterior repair (stress incontinence) day before onset of symptoms.

Year of death	Sex	Age (years)	Who certified cause of death	Necropsy performed	Died in hospital	Other admission(s)*	Hospital records examined	GP records examined	Underlying cause of death
1992	Female	54	Doctor	No	Yes	Yes	Yes	Yes	Metastatic breast cancer.
1993	Male	58	Doctor	Yes	Yes	Yes	No, excluded at outset	No, excluded at outset	Pulmonary veno-occlusive disease.
1994	Female	35	Coroner	Yes	No	No	No, excluded at outset	No, excluded at outset	Unascertained cause of death, "death by natural cause of obscure aetiology".
1994	Female	58	Doctor	Yes	Yes	Yes	No, excluded at outset	No, excluded at outset	Bilateral renal vein thrombosis.
1995	Male	45	Doctor	No	Yes	Yes	No, excluded at outset	No, excluded at outset	Chronic renal failure.
1996	Female	38	Coroner	No	Yes	Yes	Yes	Yes	Discussed with two specialists in internal medicine, insufficient evidence for diagnosis of PE.
1996	Male	55	Coroner was yet to rule	Yes	No	Yes	Yes	Yes	PE found at necropsy, but wide excision of malignant melanoma right foot and split skin graft 10 days before onset of symptoms.
1996	Female	58	Coroner	Yes	Yes	Yes	Yes	Yes	PE found at necropsy, but surgical decompression of rotator cuff right shoulder one day before onset of symptoms.
1997	Female	35	Coroner	Yes	Yes	Yes	No, excluded at outset	No, excluded at outset	Cerebral infarction.
1997	Female	44	Coroner	Yes	Yes	Yes	Yes	Yes	PE found at necropsy, but surgery to place indwelling epidural pump 28 days before onset of symptoms.

Year of death	Sex	Age (years)	Who certified cause of death	Necropsy performed	Died in hospital	Other admission(s)*	Hospital records examined	GP records examined	Underlying cause of death
1997	Male	57	Doctor	No	Yes	Overseas visitor	Yes	Overseas visitor	Discussed with two specialists in internal medicine, insufficient evidence for diagnosis of PE.
1998	Male	50	Coroner	Yes	No	Yes	Yes	Computer records deleted	PE found at necropsy, but underlying cause portal vein thrombosis.
1998	Male	53	Coroner	Yes	No	Yes	Yes	Yes	PE found at necropsy, but right-sided total hip joint replacement (osteoarthritis) 7 days before onset of symptoms.
1998	Female	58	Doctor	No	Yes	Yes	No, excluded at outset	No, excluded at outset	Budd-Chiari syndrome with secondary cirrhosis of the liver.
1998	Male	59	Coroner	Yes	No	Yes	Yes	Yes	PE found at necropsy, but left-sided total hip joint replacement (osteoarthritis) 18 days before onset of symptoms.
1999	Male	45	Coroner	Yes	No	Yes	Yes	Yes	PE found at necropsy, but surgical repair of multiple lacerations and application of bilateral below-knee plaster casts 21 days before onset of symptoms.
2000	Female	44	Coroner	Yes	Yes	Yes	Examined records from hospital in which case died. Other hospital not identified	Yes	PE found at necropsy, but laparoscopic surgery left knee 14 days before onset of symptoms.
2000	Female	48	Coroner	Yes	Dead on arrival	No	No record of arrival at hospital	Yes	History of recurrent DVT (no PE), ruptured liver secondary to anticoagulation.

Year of death	Sex	Age (years)	Who certified cause of death	Necropsy performed	Died in hospital	Other admission(s)*	Hospital records examined	GP records examined	Underlying cause of death
2000	Female	54	Coroner	No	No	No	-	Yes	Insufficient evidence for diagnosis of PE.
2000	Female	59	Coroner	Yes	No	No	-	Yes	PE found at necropsy, but breast cancer underlying cause.

* Admission to hospital at any other time in year before death.
† The date of onset of the fatal episode was taken as the index date.

Abbreviations used in the table DVT: deep vein thrombosis, GP: general practice, PE: pulmonary embolism.

2.4.2 Eligible cases

Of the 121 cases who were determined to be eligible for inclusion in the present research, 41 were male and 80 were female. Eight were short-term overseas visitors to New Zealand and 113 were normally resident in New Zealand. The underlying cause of death in 105 cases was certified by a coroner and for 16 cases a Medical Certificate of Causes of Death was completed by a doctor. The diagnosis of pulmonary embolism was confirmed by necropsy in 113 and by ventilation-perfusion scans or pulmonary angiography in four. Of the remaining four cases, two had venograms that demonstrated venous thrombosis. The two specialists in internal medicine, using standard criteria (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995a), determined that these four cases also had sufficient evidence for a diagnosis of pulmonary embolism.

For each eligible case, information from death and medical records was used to determine the date of onset of the fatal episode (the reported date on which symptoms of venous thromboembolism were first experienced or, if there was no recorded history of symptoms, the date of death). This was taken as the index or reference date. The numbers of deaths which occurred in each year of the study period are shown in Table 2.7. As can be seen, the number of cases for whom the index date fell in a particular year did not always correspond with the number of deaths for that year. This is because several cases died some days after their index date (Table 2.8).

The age distribution of the cases by sex is shown in Table 2.9. The median ages of men and women on the index date were 49.0 and 43.1 years respectively.

Table 2.7 Distribution of index dates and dates of death of eligible cases, New Zealand residents and overseas visitors

Year	Number of cases with index date in that year (n=121)	Number of cases who died in that year (n=121)
1986	1	-
1990	10	9
1991	7	8
1992	8	8
1993	13	12
1994	8	9
1995	12	10
1996	10	11
1997	18	20
1998	12	12
1999	4	4
2000	18	18

Table 2.8 Interval between onset of symptoms and death, New Zealand residents and overseas visitors

Interval between index date and date of death	Number of cases (n=121)
Died same day that symptoms began	54
1 day	10
2 days	7
3 days	5
4 days	2
5 days	4
6 days	3
7 – 13 days	12
14 – 20 days	4
21 – 27 days	5
≥ 28 days	15

Table 2.9 Age on index date and date of death by sex, New Zealand residents and overseas visitors

Age group (years)	Number of females in age group		Number of males in age group	
	On index date	On date of death	On index date	On date of death
< 20	1	1	2	2
20 – 24	5	5	1	1
25 – 29	9	9	1	1
30 – 34	12	12	3	3
35 – 39	5	4	3	3
40 – 44	11	11	5	5
45 – 49	13	14	6	6
50 – 54	11	11	11	11
55 – 59	13	13	9	9
Median age	**43.1**	**43.8**	**49.0**	**49.0**

PART II FATAL PULMONARY EMBOLISM AND THE USE OF MEDICINES

CHAPTER 3 VENOUS THROMBOEMBOLISM AND THE USE OF ORAL CONTRACEPTIVES AND PSYCHOTROPIC DRUGS

3.1 INTRODUCTION

This chapter will discuss the relationships between venous thromboembolism and two groups of medicines, oral contraceptives and psychotropic drugs. The risk of venous thromboembolism in oral contraceptive users has been extensively studied, whereas there are very few studies which have examined the risk in users of psychotropic drugs — hence the greater part of the discussion in this chapter is devoted to oral contraceptives. The discussion is also confined to data that were available before the publication of the research outlined in Chapters 4 – 6 on fatal pulmonary embolism and the use of oral contraceptives (Parkin et al. 2000) and psychotropic drugs (Parkin et al. 2003). Subsequent investigations of consequence, including two meta-analyses, are referred to in Chapter 6.

The chapter takes the form of a narrative review of the evidence which links venous thromboembolism with the use of oral contraceptives and psychotropic drugs. In addition, it considers the ways in which the evolving evidence about oral contraceptives was disseminated and the various responses to that information.

To identify relevant papers, several search strategies were employed. The Medline database was searched using the following terms: "pulmonary embolism" "thromboembolism", "venous thrombosis", "thrombophlebitis", "contraceptives, oral", "psychotropic drugs" (antidepressive agents [antidepressive agents, second-generation; antidepressive agents, tricyclic], tranquilizing agents [anti-anxiety agents, antimanic agents, antipsychotic agents]), and "hypnotics and sedatives". Terms used to search the Embase database included "venous thromboembolism", "thromboembolism", "vein thrombosis", "lung embolism", "deep vein thrombosis", "oral contraceptive agent", and "psychotropic agent" (psychostimulant agent [antidepressant agent], tranquilliser [anxiolytic agent, neuroleptic agent]). The reference lists of retrieved papers were also examined.

3.2 ORAL CONTRACEPTIVES AND VENOUS THROMBOEMBOLISM

3.2.1 Early studies and consequential action

Early studies

In 1961, soon after the introduction of oral contraceptives, a general practitioner in the UK reported a case of pulmonary embolism which "had apparently been precipitated by drug treatment" (Jordan 1961). The medicine concerned was Enavid, an oral contraceptive containing 150μg mestranol and 9.85mg norethynodrel, which had been prescribed to a 40 year old woman to treat endometriosis. The therapy consisted of one tablet taken daily for two weeks, after which the dose was increased to two tablets daily. Uncontrolled vomiting resulted and the treatment was stopped. However, several days later the woman developed pleuritic chest pain and a diagnosis of pulmonary embolism was confirmed by chest X-ray and an electrocardiograph. The general practitioner proposed that dehydration, secondary to excessive vomiting, had triggered this event and he urged that Enavid be used with caution.

This case report was followed by many more accounts of venous thromboembolism in oral contraceptive users, prompting investigations by several drug regulatory authorities. In 1963, an ad hoc committee in the USA estimated that the death rate among women taking Enovid (marketed in the UK as Enavid) was 12.1 per million users as compared with an age-standardised rate of 8.4 per million women in the general population (Ad Hoc Committee for the Evaluation of a Possible Etiologic Relation with Thromboembolic Conditions 1963). It concluded that no significant increase in mortality among Enovid users had been demonstrated, but until further data were available, a relationship between Enovid and venous thromboembolism "should be regarded as neither established nor excluded".

In the UK, following a request to doctors to report cases of venous and arterial thrombosis that occurred in women taking oral contraceptives (Cahal 1965a), the Committee on Safety of Drugs was notified of 16 deaths from such conditions in oral contraceptive users in the year to August 1965 (Cahal 1965b). Using national mortality statistics, the Committee estimated that this was not appreciably different from what would have been expected among the general population of women of child-bearing age. It was, however, noted that eight of the deaths were from pulmonary embolism,

whereas only two would have been expected. The Committee considered that "no firm conclusion can be drawn from the data at present available" and urged doctors to report all suspected adverse reactions to oral contraceptives and to ascertain whether women suffering thromboembolic events were pill users.

The following year, an advisory committee of the USA Food and Drug Administration and a scientific group convened by WHO both concluded that the available data were insufficient to confirm a causal relationship between oral contraceptive use and venous thromboembolism (Advisory Committee on Obstetrics and Gynecology 1966; World Health Organization 1966).

Meanwhile, in response to the lack of data, the Committee on Safety of Drugs in the UK initiated a case-control study of cardiovascular mortality in women of child-bearing age and sought the views of the Medical Research Council (MRC) (Inman 1970). Following recommendations from a subcommittee established by the Council, case-control studies were undertaken by the MRC Statistical Research Unit and by the Royal College of General Practitioners to explore the possible association between oral contraceptives and non-fatal cardiovascular events. In May 1967, preliminary results of these three studies were published by the MRC subcommittee which asserted that "the sum of evidence...is so strong that there can be no reasonable doubt that some types of thromboembolic disorder are associated with the use of oral contraceptives" (Medical Research Council 1967). In the opinion of the subcommittee, the association could not be explained by bias or confounding, and it concluded that "the oral contraceptives are themselves a factor in the production of the disease". The excess of deaths from pulmonary embolism among oral contraceptive users was estimated to be about three per 100,000 women per year. The details of these and other early case-control studies that explored the association between oral contraceptive use and venous thromboembolism are shown in Table 3.1.

In 1968, three cohort studies were set up to explore the health effects of oral contraceptive use: the Royal College of General Practitioners' Contraceptive Study and the Oxford / Family Planning Association Contraceptive Study in the UK and the Walnut Creek Contraceptive Drug Study in the USA. Table 3.2 provides an account of these studies.

Table 3.1 Early case-control studies of oral contraceptive use and venous thromboembolism

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information*	Results
(Royal College of General Practitioners 1967)	Total 147 cases, 294 controls VTE 87 cases (SVT, DVT, or PE unrelated to pregnancy), 174 controls	Women aged 15 – 49 years with a first episode of a venous or arterial thromboembolic disorder between 1961 and June 1966, who attended the practices of 29 UK GPs who kept disease indexes for the Records Unit and Research Advisory Service of the Royal College of General Practitioners.	2 women selected from same general practice as case. Matched by age (within 5 years), marital status, and parity.	Cases and controls interviewed by their GP. Current use of OC Use at time of onset of VTE (cases) and a date in that same year (controls). Reference category Non-users (past and never users combined).	**All venous events (SVT, DVT, PE)** 15/87 (16.5%) cases, 12/174 (6.9%) controls current users† Unadjusted unmatched OR for current OC use Any OC: 2.8† Crude incidence VTE per 100,000 woman-years OC users: 450 Non-users: 130
(Inman and Vessey 1968)	Total 309 cases, 998 controls PE or PI 77 cases (26 idiopathic, 51 had predisposing conditions), 168 controls	Married women aged 20 – 44 years normally resident in England, Wales, and Northern Ireland who died during 1966 from PE or PI, coronary thrombosis or MI, cerebral thrombosis or embolism. Identified using death certificates provided by Registrar-Generals. Excluded deaths during pregnancy and puerperium.	2 – 6 married women aged 20 – 44 years selected from the same general practice as each case.	GPs of cases and controls interviewed by medical staff from Committee on Safety of Drugs using a standardised questionnaire. Also interviewed hospital and family planning clinic Drs for cases. Current use of OC Using OCs at onset of terminal episode (cases), date of interview (controls). Reference category Non-users (never and past users combined).	**Idiopathic PE or PI** 16/26 (62%) cases, 171/998 (17.1%) controls current users. Expected number of OC users among cases, based on exposure status of controls of similar age and parity: 4.2, p-value for difference < 0.001. Unadjusted OR for current OC use Any OC: 7.7† Crude mortality rate per million woman-years OC users: 23† Non-users: 2†

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information*	Results
(Vessey and Doll 1968; Vessey and Doll 1969)‡	Total 123 cases, 246 controls DVT or PE 84 cases, 168 controls	Married women aged 16 – 40 years admitted to 19 hospitals in North-West Metropolitan region in UK between 1964 and 1967 with DVT, PE, cerebral thrombosis, or coronary thrombosis. Excluded fatal events and women who were sterilised or post-menopausal. Also those with any other predisposing chronic or acute conditions, including surgery, pregnancy, or trauma during 3 months before the event.	For each case, 2 married women admitted with an acute medical or surgical condition, or for elective surgery for a condition which would not have influenced contraceptive habits. Matched by hospital, date of admission (within 4 months), age (within 4 years), and parity. Other than surgery, same exclusion criteria as for cases.	Cases and controls interviewed by medical social worker at home using a standardised questionnaire (apart from a few who completed a postal questionnaire). Current use of OC Use in month before admission. Reference category Non-users (never and past users combined).	**DVT or PE, all women** 42/84 (50%) cases and 23/168 (14%) controls current users. P-value for difference (allowing for matching) < 0.001. Unadjusted unmatched OR (95% CI) for current OC use Any OC: 6.3 (3.4 – 11.6). **DVT or PE, excluding women with previous events** 30/55 (55%) cases and 20/159 (13%) controls current users. P-value for difference (allowing for matching) < 0.001. Unadjusted unmatched OR for current OC use Any OC: 8.3† Crude hospitalisation rate for DVT or PE per 100,000 women per year OC users: 45 Non-users: 5

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information*	Results
(Sartwell et al. 1969; Sartwell 1971)‡	Total 175 cases, 175 controls VTE 145 cases (27 SVT, 118 DVT or PE), 145 controls	Married women aged 15 – 44 years admitted to 43 hospitals in USA over 3-year period with SVT, DVT, PE, or cerebral thrombosis or embolism. In one centre unmarried women also included. Excluded fatal events, and women who were sterilised, post-menopausal, or had conditions considered to be contraindications to OC use or to pregnancy. Also those with previous venous or arterial vascular events; other predisposing chronic conditions; obesity; childbirth, surgery, or major trauma within 6 weeks of the event; systemic infection within 4 weeks; minor infection, trauma or inflammation within 2 weeks; and unusually strenuous physical activity or immobility within 2 weeks.	For each case, 1 woman admitted with an acute medical or surgical condition, trauma, or for elective nose or throat surgery (2 controls selected for each case, only 1 used). Matched by hospital, date of admission (within 6 months), age (5-year bands), parity, ethnicity, residence, payment status. Also by marital status. Other than surgery, same exclusion criteria as for cases.	Married cases and controls interviewed by market researchers, unmarried women by students from a women's medical college. All participants interviewed at home using a standardised questionnaire. Current use of OC Use in month before admission. Reference category Non-users (never and past users combine).	**SVT** Matched OR for current OC use Any OC: 3.0† **DVT or PE** Matched OR for current OC use Any OC: 4.2† 29/118 (25%) cases of DVT or PE attributable to OC use† **PE only** 7/18 cases used sequential preparations. No controls used these products.

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information*	Results
(Vessey et al. 1970)	30 cases, 60 controls	Married women aged 16 – 40 years admitted between 1964 and 1967 to same 19 hospitals as in previous research by Vessey and Doll (1968 and 1969) and to hospitals in Oxford region in UK with DVT or PE ≤ 1 month after acute or elective surgery for a condition which would not have influenced contraceptive habits. Excluded fatal events, and women who were sterilised or post-menopausal. Also those with any other predisposing chronic or acute conditions, including pregnancy during 3 months before the event.	For each case, 2 married women who had undergone acute or elective surgery as for cases. Matched by year of admission, age (within 5 years), and parity. For cases in North-West Metropolitan region, controls selected from among 168 controls included in previous research. In Oxford region, selected from hospitals in same area. Same exclusion criteria as for cases.	Cases and controls interviewed by medical social worker at home using a standardised questionnaire (apart from a few who completed a postal questionnaire). Current use of OC Use in month before surgery. Reference category Non-users (never and past users combined).	**DVT or PE** 12/30 (40%) cases and 9/60 (15%) controls current users. P-value for difference (allowing for matching) = 0.01. Unadjusted unmatched OR for current OC use Any OC: 3.8 Crude incidence per 100,000 women in month post-appendectomy OC users: 3,000 Non-users: 800

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information*	Results
(Böttiger and Westerholm 1971)	Total 111 cases DVT 84 cases No controls selected	Women aged 15 – 44 years admitted between 1964 and 1968 to selected hospitals in Sweden with a venous or arterial thromboembolic disorder. Excluded those with predisposing illnesses.	Nil	Cases sent a postal questionnaire. Used OC sales data for comparisons with cases. Exposure OC use in an unspecified period before admission (cases).	**DVT** 55/84 (65%) cases using OCs compared with an average of 11% of women in same region during same period. Number of observed cases using OCs in each year exceeded expected based on population sales data (p-value < 0.001).
(Greene and Sartwell 1972)	60 cases, 60 controls	Caucasian women who were excluded from 1969 study by Sartwell et al because SVT, DVT, or PE had occurred following surgery, trauma, systemic infection, or immobilisation.	For each case, 1 Caucasian control selected from group of controls initially selected but not used in earlier study. Matched by hospital, date of admission (within 12 months), age (within 10 years), ethnicity, marital status, and severity of event that precipitated VTE in cases.	Cases and controls sent a postal questionnaire. Completed questionnaires returned by 65% cases and 63% controls. Current use of OC Use in month before admission. Reference category Non-users (never and past users combined).	**All venous events (SVT, DVT, PE)** Unadjusted matched OR for current OC use Any OC: 6.5, p-value = 0.007

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information*	Results
(Boston Collaborative Drug Surveillance Program 1973; Lawson et al. 1977)‡	43 cases, 842 controls	Women aged 20 – 44 years admitted to 24 hospitals in Boston region during 1972 with SVT, DVT, or PE. Excluded fatal events, those too ill to be interviewed, admissions < 72 hours, and women who were sterilised, post-menopausal, or pregnant. Also those with any other predisposing chronic conditions and conditions in which OCs contraindicated, and those admitted in preceding 3 months.	Women aged 20 – 44 years admitted to same hospitals with acute illness or for elective surgery. Same exclusion criteria as cases, plus women admitted with conditions that might have been related to OC use.	Cases and controls interviewed in hospital by research nurses. Current use of OC Use in 3 months before admission. Reference category Non-users (never and past users combined).	**All venous events (SVT, DVT, PE)** 31/43 (72%) cases and 170/842 (20%) controls current users. Age-adjusted OR (95% CI) for current OC use Any OC: 11.0 (5.2 – 25.0) Crude incidence VTE per 100,000 women per year OC users: 66 Non-users: 6

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information*	Results
(Stolley et al. 1975; Maguire et al. 1979)‡	461 cases, 1302 controls VTE 88 idiopathic cases, 335 controls with no predisposing factors. 318 non-idiopathic cases, number of controls not stated.	Women aged 15 – 49 years admitted to 37 hospitals in USA between 1970 and 1973 with venous and arterial thromboembolic disorders including, phlebitis and thrombophlebitis of lower limbs and other sites, PE, PI, other venous thrombosis and embolism, arterial thrombosis and embolism (excluding intracranial), and acute MI. Excluded fatal events, and women who were sterilised, post-menopausal, or had conditions considered to be contraindications to OC use or to pregnancy. Also those with previous venous or arterial vascular events, other predisposing chronic conditions, recent surgery or major trauma, and pregnant or gave birth < 30 days earlier.	For each case, 1 – 3 women admitted to same hospitals for acute or chronic medical conditions, acute or elective surgery. Matched by date of admission (within 14 months), age, ethnicity, marital status.	Cases and controls interviewed in hospital by medically-trained researchers. Current use of OC OC use in month before admission. Reference category Non-users (never and past users combined).	**Adjusted OR (95% CI) for current OC use** Idiopathic SVT, DVT Any OC: 5.0 (2.4 – 10.3) Idiopathic SVT, DVT, PE Any OC: 4.1 (1.3 – 13.1) Idiopathic PE Any OC: 6.4 (2.7 – 15.3) Non-idiopathic SVT, DVT Any OC: 1.5 (0.9 – 2.6) Non-idiopathic SVT, DVT, PE Any OC: 2.0 (1.1 – 3.8) Non-idiopathic PE Any OC: 3.4 (1.9 – 5.9) All ORs adjusted for age, ethnicity, weight, parity, marital status, centre, hospital pay status, family income, and whether patient or husband employed in medical setting.

* Including information about the use of oral contraceptives, demographic data, medical history, and other risk factors for venous thromboembolism.
† Derived from data presented in the paper.
‡ The methods and findings of the most recent paper are reported if these superseded those of the earlier publication.

Abbreviations used in the table Drs: doctors, DVT: deep vein thrombosis, GP: general practitioner, MI: myocardial infarction, OC: oral contraceptive, OR: odds ratio, PE: pulmonary embolism, PI: pulmonary infarction, SVT: superficial venous thrombosis, VTE: venous thromboembolism.

Table 3.2 Early cohort studies of oral contraceptive use and venous thromboembolism

Reference	Participants	Exposure and outcome information	Incidence per 100,000 woman-years (number of events)*	Relative risk*
(Royal College of General Practitioners 1974; Royal College of General Practitioners 1977; Royal College of General Practitioners 1978; Royal College of General Practitioners 1981; Kay 1984)* Royal College of General Practitioners' Oral Contraceptive Study	Study population 46,000 married (or living as married) women of child-bearing age recruited by 1,400 GPs in UK between April 1968 and July 1969. OC users 1st 2 women in calendar month for whom GP wrote a 1st or repeat OC prescription (n=23,000). Excluded women using OCs for non-contraceptive purposes. Women who subsequently stopped taking OCs classified as past users. If later restarted OCs, were censored at that time. Comparison group For each user, one woman who had never used OCs randomly selected from GP records, matched by age within 3 years (n=23,000). Never users who commenced OCs after recruitment were thereafter classified as users. An additional 1,000 never users selected to replace these women.	Information about all women provided by GPs every 6 months, including contraceptive use, pregnancy, all new illnesses, and death. VTE classified as idiopathic if occurred in absence of previous history, pregnancy, other predisposing events such as surgery within 4 weeks, and other serious debilitating illness. Only first episodes counted in estimation of rates.	**Adjusted incidence, idiopathic events** SVT OC users: 186 (67) Never users: 77 (36) DVT OC users: 82 (30) Never users: 20 (9) PE OC users: 19 (6) Never users: 8 (4) VT other sites OC users: 29 (12) Never users: 10 (4) **Adjusted PE mortality rate per million woman-years** OC users: 28 (3) No deaths from PE in never users Rates adjusted for age, parity, social class, and smoking.	**Adjusted RR (95% CI) for current OC use:** Idiopathic SVT Any OC: 2.4 (1.4 – 2.7) Idiopathic DVT Any OC: 4.2 (2.1 – 10.9) Idiopathic PE Any OC: 2.4 NS Idiopathic VT other sites Any OC: 2.9 NS Never users as reference. RRs adjusted for age, parity, social class, and smoking. Increasing SVT incidence with increasing oestrogen dose, DVT data too few to examine relationship with dose. For fixed dose of EE (50μg), increasing SVT incidence with increasing dose of norethisterone, DVT data too few to examine relationship with dose.

Reference	Participants	Exposure and outcome information	Incidence per 100,000 woman-years (number of events)*	Relative risk*
(Grounds 1974)	Study population Unspecified number of women of child-bearing age selected from Australian general practices in 1968. OC users Users were 1st 2 women seen by GP in calendar month who were known to be taking an OC. Only those women who attended follow-up appointment 1 year after recruitment (n=829) were included in study. Of these, 541 attended 2-year follow-up. Comparison group For each user, unsuccessfully attempted to select next 4 women of about the same age who were seen by GP and who were not taking an OC. Only those women who attended follow-up appointment 1 year after recruitment (n=746) were included in study. Of these, 507 attended 2-year follow-up.	Women followed for 2 years, interviewed annually by GPs. Asked "have you had any trouble with clots in the veins in the past year?" Also questions about other medical conditions, blood pressure and weight measured.	**Crude incidence "spontaneous venous thrombosis"** OC users: 765 (8) Non-users: 2314 (29) Events were mostly superficial thromboses in varicose veins.	**Unadjusted RR for OC use at recruitment and 1-year follow-up** Spontaneous VT Any OC: 0.33, p-value < 0.01 Non-users (at recruitment and 1-year follow-up) as reference.

Reference	Participants	Exposure and outcome information	Incidence per 100,000 woman-years (number of events)*	Relative risk*
(Vessey et al. 1976; Vessey et al. 1977; Vessey 1978a; Vessey et al. 1981; Vessey and Lawless 1984; Vessey et al. 1986)* Oxford / Family Planning Association Contraceptive Study	Study population 17,032 married Caucasian British subjects aged 25 – 39 years, recruited at 17 family planning clinics in England and Scotland between 1968 and 1974, who were users of OCs, diaphragms, or IUDs. OC users 56% of participants at recruitment. Comparison group Non-users of OCs: never users (users of diaphragms or IUDs at recruitment) plus past users (OC users at recruitment but later stopped).	Information about contraceptive use, pregnancy, hospital admissions, and outpatient treatment obtained annually from women during clinic visits or by postal questionnaires. Deaths identified using NHS central registries. Only first episodes VTE counted in estimation of incidence, VTE in association with pregnancy or puerperium excluded. VTE incidence estimated for 2 groups: 1. VTE not associated with surgery (n=71) 2. VTE during 3 months following surgery (n=34)	**Crude incidence certain/probable DVT or PE unrelated to surgery** Users of OCs with ≥ 50µg oestrogen: 62 (20) Users of OCs with < 50µg oestrogen: 39 (3) **Crude incidence possible DVT or PE unrelated to surgery** Users of OCs with ≥ 50µg oestrogen: 28 (9) No possible DVT or PE in women using OCs with < 50µg oestrogen **Adjusted incidence, events unrelated to surgery** SVT OC users: 21 (8) Non-users: 15 (17) Certain/probable DVT or PE OC users: 43 (23) Non-users: 6 (6) Possible DVT or PE OC users: 22 (10) Non-users: 7 (7) Rates adjusted for age, smoking, and history of varicose veins.	**Adjusted RR for current OC use** SVT unrelated to surgery Any OC: 1.4, NS Certain or probable DVT or PE unrelated to surgery Any OC: 7.2, p-value < 0.001 Possible DVT or PE unrelated to surgery Any OC: 3.1, p-value < 0.02 Post-operative SVT, DVT, or PE Any OC: 1.9, NS Non-users as reference. RRs adjusted for age, smoking, and history of varicose veins.

Reference	Participants	Exposure and outcome information	Incidence per 100,000 woman-years (number of events)*	Relative risk*
(Ramcharan 1974; Petitti et al. 1978; Petitti et al. 1979)* Walnut Creek Contraceptive Drug Study	Study population 16,579 women aged 18 – 54 years who were members of the Kaiser-Permanente Medical Care Program and who sought a gynaecological or general health check-up at the Walnut Creek Clinic between 1969 and 1971. At recruitment women classified as current OC users, past OC users, never users, pregnant or in puerperium, or HRT users.	Information about contraceptive use, pregnancy, non-contraceptive oestrogen use, and hospital admissions obtained through baseline and annual examinations or postal questionnaires. Information also sought from inpatient and outpatient records at Kaiser-Permanente Medical Center and other hospitals, and from death certificates. **Nested case-control analysis** Based on 38 cases and 8,174 controls matched by year of birth and calendar year. 17/38 cases idiopathic (no recent surgery, trauma, pregnancy, malignancy, past VTE, varicose veins, hypertension, or diabetes), including 2 with retinal vein thrombosis. Current use of OC Use in month before index date (date case admitted or died). Reference category Non-users (never and past users combined).	Not reported.	**Unadjusted matched OR (95% CI) for current OC use (nested case-control analysis)** All VTE events Any OC: 1.9 (0.9 – 4.1) Idiopathic VTE events Any OC: 7.6 (2.9 – 19.9) Non-users as reference.

* The methods and findings of the most recent paper are reported if these superseded those of the earlier publication.

Abbreviations used in the table DVT: deep vein thrombosis, GP: general practitioner, HRT: hormone replacement therapy, IUD: intrauterine device, NHS: National Health Service, NS: not significant, OC: oral contraceptive, OR: odds ratio, PE: pulmonary embolism, RR: relative risk, SVT: superficial venous thrombosis, VT: venous thrombosis, VTE: venous thromboembolism.

Early support for the postulated causal relationship between oral contraceptives and venous thromboembolism was not confined to the case-control and cohort studies just outlined in Tables 3.1 and 3.2. Reviews of mortality trends, which demonstrated an increase in deaths from venous thromboembolism among women of child-bearing age concurrent with an increase in contraceptive sales in the UK (Vessey and Weatherall 1968; Vessey and Inman 1973), USA (Markush and Seigel 1969; Seigel and Markush 1969), and Canada (Anderson 1970), were also compatible with a link. In addition, an increased risk of venous thromboembolism was described in other situations involving the administration of oestrogens, such as the suppression of lactation (Daniel et al. 1967; Jeffcoate et al. 1968) and the treatment of arterial disease (Oliver and Boyd 1961; The Coronary Drug Project Research Group 1970). In young women undergoing emergency surgery, radioactive fibrinogen uptake tests revealed that current users of oral contraceptives were more likely to develop post-operative deep vein thrombosis than non-users (Sagar et al. 1976). In other laboratory-based studies, prothrombotic changes were described in the blood of women taking oral contraceptives, although the findings were not always consistent (Poller 1978).

Following a suggestion that sequential oral contraceptive preparations[1] might carry a higher risk of venous thromboembolism (Sartwell et al. 1969), and the publication of a clinical trial in which thrombophlebitis of the leg veins occurred more often in those oral contraceptive users who were taking preparations with relatively high doses of oestrogens and low doses of progestogens (Grant 1969), a review was undertaken of spontaneous reports to the Committee on Safety of Drugs in the UK, the Swedish Adverse Drug Reaction Committee, and the Danish National Health Service's Board on Adverse Reactions to Drugs (Inman et al. 1970). Using oral contraceptive sales data and assuming that all preparations carried the same risk of venous thromboembolism, the number of expected events was estimated for each product and compared with the observed number of cases. The investigators found no evidence that sequential preparations carried a higher risk of venous thromboembolism than non-sequential

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[1] Preparations in which oestrogen-only tablets were taken for 14 – 16 days, followed by a five to seven day course of tablets containing both oestrogen and progestogen.

products containing the same doses of oestrogen. However, they did find an excess of observed cases for oral contraceptives containing higher doses of oestrogen in all three countries. Moreover, in a pooled analysis of three case-control studies which individually had shown no evidence of a dose-response relationship (Inman and Vessey 1968; Sartwell et al. 1969; Vessey and Doll 1969), oral contraceptives with higher doses of oestrogen were associated with a greater risk of venous thromboembolism. After considering several possible biases, the researchers concluded there was "no doubt" that the apparent dose-response relationship was real. The data about progestogens were less clear cut; it was thought that an observed excess of cases who were users of oral contraceptives containing megestrel and a deficit of cases using pills containing norethynodrel might indicate that the progestogen component had some influence in thrombogenesis, but alternative explanations for the findings could not be ruled out.

Preliminary findings from this study prompted a decision by the Committee on Safety of Drugs to issue an early warning about the higher risk of venous thromboembolism with higher oestrogen doses and to recommend that oral contraceptives containing more than 50μg of oestrogen (ethinyloestradiol or mestranol) should not normally be prescribed (Scowen 1969a). The Committee later explained its reasoning for this decision, stating that it "did not feel that it could delay for months for a detailed analysis of the individual preparations, since during each month several women would die unnecessarily and many more would suffer from avoidable hazard" (Committee on Safety of Drugs 1970). Unfortunately, information about the impending early warning was leaked to the media in the UK following a confidential meeting with oral contraceptive manufacturers, forcing the Committee to make a public announcement in December 1969 before doctors had received its planned communication (Scowen 1969b). In the wake of the media publicity, many women in the UK stopped taking oral contraceptives (Badaracco et al. 1973; Royal College of General Practitioners 1974), thousands of unintended pregnancies were thought to have occurred (Badaracco et al. 1973), and the Committee received much criticism from the medical profession for its handling of the matter (Editorial 1969; Editorial 1970a). In Sweden, the source of some of the published data, doctors were also advised to prescribed oral contraceptives with the lowest possible dose of oestrogen, however there was only a slight reduction in the estimated proportion of women of child-bearing age who were using oral contraceptives in 1970 (Böttiger et al. 1980).

In the USA, the issue received widespread coverage in the media (Phillips 1974), but this did not appear to result in any immediate reduction in the proportion of married women using oral contraceptives in the general population (Westoff 1976) or among those participating in the Walnut Creek cohort study (Phillips 1974).

In New Zealand, too, the response was quite different from that of the UK. In August 1969, the New Zealand Committee on Adverse Drug Reactions reported that it had been notified of several deaths and non-fatal episodes of venous thromboembolism in women taking oral contraceptives (New Zealand Committee on Adverse Drug Reactions 1969). A few months later, the New Zealand Medical Journal carried an editorial which outlined the results of the recently published UK study (Editorial 1970b), as well as a communication from the Committee on Adverse Reactions to Drugs about a similar excess of venous thromboembolic events among oral contraceptive users in New Zealand who were taking preparations with higher doses of oestrogen (McQueen 1970). Subsequently, there was a notable absence of correspondence in the New Zealand Medical Journal about these reports and there appeared to be no evidence that a "pill scare" had eventuated.

From controversy to consensus

At first, the existence of a relationship between oral contraceptives and venous thromboembolism was not universally accepted. Researchers working for the pharmaceutical company which developed the first oral contraceptive were quick to dismiss the evidence for a link by citing biases in the epidemiological studies and presenting data from clinical trials which did not find a relationship (Drill and Calhoun 1968; Drill and Calhoun 1969; Drill 1972a; Drill 1972b). Similarly, doctors known to work for two other oral contraceptive manufacturers proposed alternative explanations for the association, although the possibility that oral contraceptive users might have a slightly elevated risk of venous thromboembolism was not ruled out (Preston 1971; Zador 1976). Other commentators also suggested that various biases and confounding might have distorted the results of the published epidemiological studies (Haeger et al. 1967; Crombie and Cross 1969; Hougie 1969; Moses 1969; Nanni 1970; Goldzieher and Dozier 1975). Furthermore, a randomised controlled trial which appeared to show that the risk of venous thromboembolism was not increased in oral contraceptive users

(Fuertes-de la Haba et al. 1971) was taken as evidence that the findings of the observational studies were spurious (Hougie 1973).

However, doubts were soon expressed about the methods of the randomised controlled trial and little weight was given to the results (McQueen 1971). Meanwhile, successive reviews of the emerging evidence from other epidemiological studies led researchers and commentators in the UK (Doll and Vessey 1970; Bradford Hill 1974; Vessey 1974; Vessey and Doll 1976; Vessey and Mann 1978; Vessey 1978b; Vessey 1980), USA (Meeker 1969; Sartwell 1972; Handin 1974; Stolley 1978; Prentice and Thomas 1987), and New Zealand (McQueen 1971; McQueen 1978) to conclude that the observed association between oral contraceptive use and venous thromboembolism was real and that it reflected a causal relationship.

In 1981, a comprehensive review of the relationships between oral contraceptive use and venous (Stadel 1981a) and arterial (Stadel 1981b) cardiovascular disease summarised the current knowledge about oral contraceptive use and venous thromboembolism as follows. First, current use of oral contraceptives was associated with an increased risk of venous thromboembolism, as well as arterial cardiovascular diseases such as myocardial infarction and stroke. Second, the risk of venous thromboembolism progressively increased during the first month of use and then remained constant. The risk declined during the first month following discontinuation of oral contraceptives and then returned to the background risk found in never users. Third, compared with non-users, women without pre-existing risk factors who were current users of oral contraceptives had a 4- to 11-fold increased risk of venous thromboembolism. The relative risks found in cohort studies tended to be somewhat lower than those found in case-control studies, possibly because participation in the studies might have influenced doctors' prescribing habits. Fourth, the association between oral contraceptives and venous thromboembolism was weaker in women with other risk factors, although the attributable risk was higher than for idiopathic events. Compared with non-users, oral contraceptive users had a two-fold increased risk of post-operative venous thromboembolism. The association between oral contraceptive use and venous thromboembolism was not modified by age, parity, or socio-economic status. There were conflicting data about weight and smoking, but it was thought unlikely that they had any important effect on the association. It appeared that ABO

blood group type might modify the risk. Fifth, a dose-response relationship had been found for the oestrogen component of the pill. However, while a few studies had suggested that the progestogen component might have some role in thrombosis, no clear association between the progestogen content of most oral contraceptives had been established. Sixth, in the UK the annual incidence of symptomatic superficial or deep vein thrombosis for healthy women of child-bearing age was estimated to be 3 per 1,000 in oral contraceptive users and 1 per 1,000 in non-users. Seventh, although oral contraceptive use increased the risk of dying from pulmonary embolism, the mortality rate was very low. Finally, various haematological, biochemical, and physiological changes in oral contraceptive users had been reported which might explain the increased risk of venous and arterial thrombotic events.

Changes in prescribing practices and oral contraceptive formulations

Following the announcement by the UK Committee on Safety of Drugs in December 1969, prescribing practices changed rapidly and by May 1970, very few women in the UK were using oral contraceptives containing more than 50µg of oestrogen (Badaracco et al. 1973). A similar trend was observed elsewhere; by 1974 most pill users in many countries were taking preparations containing 50µg of oestrogen (Doll 1974). Emerging information about other serious adverse reactions, such as myocardial infarction (Inman and Vessey 1968; Mann and Inman 1975; Mann et al. 1975; Mann et al. 1976a; Mann et al. 1976b; Jick et al. 1978a; Jick et al. 1978b) and stroke (Inman and Vessey 1968; Vessey and Doll 1968; Vessey and Doll 1969; Collaborative Group for the Study of Stroke in Young Women 1973; Royal College of General Practitioners 1974; Jick et al. 1978c), also served to encourage more selective prescribing of oral contraceptives (Sartwell and Stolley 1982). Thus, older women with other risk factors for cardiovascular disease were less likely to be prescribed oral contraceptives than previously (Thorogood and Vessey 1990).

Major changes were also made to the formulation of oral contraceptives in an effort to reduce the risk of arterial and venous vascular events, as well as some of the so-called minor side effects associated with pill use. The dose of oestrogen was progressively lowered from 50µg to 30µg, and then to 20µg. New progestogens were also developed; levonorgestrel was introduced onto the market in the late 1960s (Newton 1995), and in the 1980s the so-called third generation oral contraceptives were released on to the

market (Fotherby and Caldwell 1994). These latest preparations contained either 30μg or 20μg of ethinyloestradiol and one of two new progestogens — desogestrel and gestodene. One other new progestogen, norgestimate, was introduced around the same time. Oral contraceptives containing this progestogen have rather inconsistently been classified as third generation pills (because of the timing of their introduction), while at other times they have been grouped with levonorgestrel preparations (because norgestimate is reportedly metabolised to levonorgestrel) (Newton 1995). This highlights a confusing practice — oral contraceptives have been categorised by the date of introduction, the chemical structure or dose, and sometimes the rationale for a classification system has been unclear (Petitti 2003).

Several reviews suggested, on the basis of haematological and biochemical studies, that oral contraceptives containing desogestrel and gestodene had less adverse impact on the coagulation system and carbohydrate metabolism than other low-dose preparations (< 50μg oestrogen), although it was also noted that some of the reviewed studies suffered from methodological problems (Speroff et al. 1993; Fotherby and Caldwell 1994; Newton 1995). Other metabolic studies also suggested that the new pills were less androgenic and, although individual progestogens appeared to have differing effects on various lipids, overall the effects on lipoprotein metabolism were less unfavourable than those seen with older products (Speroff et al. 1993; Fotherby and Caldwell 1994; Newton 1995). Few conclusions were drawn about the metabolic effects of norgestimate as the available data were limited.

Most of the reviewers urged that these apparently beneficial metabolic effects should be interpreted with caution. One group stressed that the clinical relevance of the findings was uncertain and that epidemiological studies were required to confirm any advantages of the new progestogens (Speroff et al. 1993). Others pointed out that although it appeared that the new oral contraceptives were an improvement on the older low-dose pills, "this conclusion has to be viewed against the background of many years of use of the other low-dose COCs, which appear not to have resulted in a high incidence of undesirable side-effects" (Fotherby and Caldwell 1994).

Nonetheless, the new preparations containing desogestrel and gestodene were marketed as having a better cardiovascular safety profile than older low-dose pills. Indeed, it was

even suggested that the use of these preparations might turn out to be, as was (supposedly) the case with hormone replacement therapy, protective against arterial cardiovascular disease (Samsioe and Mattsson 1990). The new products were also advertised as causing fewer troublesome side effects such as weight gain, mood changes, acne, and other androgenic effects, than older preparations (Stockbridge 1998). Desogestrel pills were also promoted for use by peri-menopausal women (Stockbridge 1998). The uptake of these oral contraceptives was rapid; in the four years between 1988 and 1992 the market share in European countries increased from about 30% to over 60% (Fotherby and Caldwell 1994).

3.2.2 The need for new studies of oral contraceptive safety

Uncertainty about the risk of venous thromboembolism in contemporary users of new preparations

In the 1980s it became clear that there was a need for new studies of oral contraceptive safety (Poulter et al. 1991). At the start of the decade most of the available data were derived from studies in which women were taking higher dose oral contraceptives and it was uncertain whether changes in the formulation of oral contraceptives and more selective prescribing practices had resulted in any reduced risk of venous thromboembolism in users (Stadel 1981a; Sartwell and Stolley 1982). Moreover, a few commentators remained doubtful about the reliability of the relative risk estimates obtained in the earlier research because of the small size of many of the studies, the lack of objective diagnostic tests, and various other biases which they suggested had inflated the relative risks to an unknown degree (Realini and Goldzieher 1985).

As the decade progressed, new studies were published but much uncertainty remained. For example, evidence about the benefits of lower oestrogen doses was inconsistent. In Sweden, a comparison of official morbidity statistics in two periods (1966 to 1968 when oral contraceptives all contained $\geq$ 75µg oestrogen and 1974 to 1976 when pills containing > 50µg oestrogen had been withdrawn from the market) showed a reduction in hospital admissions for idiopathic venous thromboembolic disorders among women of child-bearing age during the later period, although there were no differences in mortality (Böttiger et al. 1980). The findings of an earlier study of deaths from pulmonary embolism in young women between 1960 and 1972, were suggestive of a

decline in mortality concurrent with the reduced use of very high-dose oral contraceptives (Sartwell et al. 1976).

A review of spontaneous reports to the UK Committee on Safety of Drugs of cardiovascular events in users of oral contraceptives, which used similar methods to an earlier study (Inman et al. 1970), showed that there were fewer deaths from venous thromboembolism between 1974 and 1977 than expected among women using oral contraceptives containing 30μg oestrogen, assuming that 30μg and 50μg pills carried the same risk (Meade et al. 1980). However, no such difference was found for non-fatal events and it is difficult to know what impact under-reporting might have had on the results. An analysis of the role of progestogens in cardiovascular disease showed that for a fixed dose of oestrogen, the risk of stroke and myocardial infarction increased with increasing doses of norethisterone. The risk of venous thromboembolism, however, appeared unaffected by progestogen dose.

Results from the Oxford / Family Planning Association Contraceptive Study also suggested that oral contraceptives containing < 50μg of oestrogen carried a lower risk of venous thromboembolism than pills containing ≥ 50μg oestrogen, although the data were too few to draw a definite conclusion (Vessey et al. 1986). In the Royal College of General Practitioners' Study of Contraception, a dose-response was found for superficial venous thrombosis, but there were insufficient data to examine the relationship for deep venous thrombosis (Royal College of General Practitioners 1978). In a retrospective cohort study based on the Michigan Medicaid population, users of oral contraceptives containing 50μg and > 50μg oestrogen both had a higher incidence of venous thromboembolism than women taking pills containing < 50μg oestrogen; the adjusted relative risks were 1.5 (95% CI 1.0 – 2.1) and 1.7 (95% CI 0.9 – 3.0) respectively (Gerstman et al. 1991). An earlier analysis suggested that the relative oestrogen potency of oral contraceptive preparations (based on the dose of ethinyloestradiol or mestranol, the type and dose of progestogen, and the possible interactions between the two hormones) also played a role; low-oestrogen potency oral contraceptives carried a lower risk of venous thromboembolism than intermediate or high-oestrogen potency formulations (Gerstman et al. 1990). No such dose-response was observed in relation to progestogen potency.

In laboratory-based studies, adverse changes in coagulation activity were reported to be less marked in women taking oral contraceptives containing 30μg of oestrogen than in users of 50μg pills (Bonnar 1987). In addition, for a given dose of oestrogen, the magnitude of coagulation changes varied with the type of progestogen.

Conversely, other investigators reported that oral contraceptives containing different doses of oestrogen appeared to carry comparable risks of venous thromboembolism (Porter et al. 1982; Helmrich et al. 1987). Moreover, the estimates of risk in oral contraceptive users relative to non-users were very similar in magnitude to those found in the early studies. In a case-control study based on 61 cases and 1278 controls aged 18 – 49 years, who were admitted to American and Canadian hospitals between 1976 and 1983, the use of oral contraceptives in the month before admission was associated with a nine-fold increased risk of non-fatal venous thromboembolism (Helmrich et al. 1987). It should, however, be noted that there was a wide confidence interval around this estimate (adjusted odds ratio 8.8 [95% CI 3.6 – 22.0]).

Similarly in a cohort study based on women aged 20 – 44 years who were members of the Group Health Cooperative of Puget Sound during a three-year period between 1977 and 1979, the incidence of idiopathic non-fatal venous thromboembolism in current users of oral contraceptives was reported to be about eight times that of non-users (Porter et al. 1982). In a later analysis involving women in the Group Health Cooperative who were aged 15 – 44 years between 1980 and 1982, oral contraceptive users were reported to have a three to five-fold increased risk (Porter et al. 1985). The investigators later reported that the women-years at risk for oral contraceptive users had been overestimated for both study periods (Porter et al. 1987); hence, it is likely that the relative risks were underestimated. It should also be noted, however, that the numbers of venous thromboembolic events during both study periods were small (10 and nine respectively).

Uncertainty about the risk of venous thromboembolism in oral contraceptive users in other countries

Almost all of the early and subsequent studies which had shown a relationship between oral contraceptive use and venous thromboembolism (as well as other cardiovascular events) were undertaken in the UK, USA, Canada, and Scandinavian countries.

Consequently there was some concern that this information might not be generalisable to populations with different background risks of venous thromboembolism, and different economic and environmental conditions (Poulter et al. 1991). Hence, there was a need for epidemiological studies in other countries — especially countries in which the balance of risks and benefits of oral contraceptives might differ from Western nations. A hospital-based case-control study undertaken in Mexico, Hong Kong, and the German Democratic Republic had insufficient power to examine the risk of cardiovascular disease by country (World Health Organization Collaborative Study 1989).

Other gaps in knowledge

The early studies of oral contraceptive safety had been unable to provide certain important information for oral contraceptive users and prescribers. For example, there was very little information about the risks of venous thromboembolism in relation to the duration of use and the previous use of oral contraceptives (Poulter et al. 1991). In addition, previous studies had lacked power to determine whether the presence of other factors, such as smoking, modified the relationship between oral contraceptives and venous thromboembolism.

3.2.3 Initiation of new research and early responses

The new studies

WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception

In response to the need for more information about the safety of various contraceptive methods, the Special Programme of Research, Development, and Research Training in Human Reproduction (established by WHO) formed a Task Force on the Safety and Efficacy of Fertility Regulating Methods (Skegg 1999). In 1985, a steering committee for the Task Force identified nine priority areas for research, including cardiovascular disease and hormonal contraception. Subsequently, after a pilot study, the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception was initiated in 21 centres in Africa, Asia, Europe, and Latin America to determine whether modern oral contraceptives, as they were currently prescribed, were associated with increased risks of venous thromboembolism, myocardial infarction, or stroke (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid

Hormone Contraception 1995a). An additional aim in each of the three hospital-based case-control studies was to ascertain whether any such risks differed between Europe and countries in three other regions (Africa, Asia, Latin America and the Caribbean). Secondary aims were to explore the risks in sub-groups of women (such as past users and those with pre-existing risk factors) and to establish whether different oral contraceptive preparations carried different risks of cardiovascular disease.

Transnational study

In 1989, the results of a German pharmacokinetic study were published which raised concerns about the safety of oral contraceptives containing gestodene (Jung-Hoffmann and Kuhl 1989). In this study, 22 volunteers were randomly assigned to take an oral contraceptive containing 30μg of ethinyloestradiol with either 75μg gestodene or 150μg desogestrel for a period of 12 months. Blood samples, which were taken on days one, 10, and 21 during the first, third, sixth, and twelfth cycles, showed significantly higher levels of serum ethinyloestradiol in women taking the gestodene preparation. This finding prompted German regulatory authorities to issue an alert to doctors and to request that an epidemiological study be undertaken to investigate the cardiovascular safety of oral contraceptives containing this progestogen (Spitzer et al. 1996). After some input from investigators involved in the WHO study, the Transnational hospital-based case-control study was initiated with funding provided by a pharmaceutical company.

The UK General Practice Research Database and Leiden studies

Early in 1995, an analysis of the WHO study unexpectedly showed a doubling of risk of venous thromboembolism in users of desogestrel and gestodene oral contraceptives, relative to users of older preparations (Farley et al. 1999). No plausible alternative explanations for the excess risk, which was confirmed in a more detailed analysis, were identified. The finding was discussed at an urgent consultation meeting in Geneva in July 1995, which was attended by investigators from the Transnational study, oral contraceptive manufacturers, and regulatory authorities. An expeditious analysis of the Transnational study was requested and researchers from the Boston Collaborative Drug Surveillance Program agreed to undertake an epidemiological study using the UK General Practice Research Database (GPRD) (Rawlins 1995). A reanalysis of the Leiden Thrombophilia Study was also initiated.

Announcement by the UK Committee on Safety of Medicines

On 18 October 1995, on the basis of unpublished data from the WHO, GPRD, and Transnational studies discussed above, the Committee on Safety of Medicines (CSM) in the UK issued a warning that low-dose oral contraceptives containing desogestrel and gestodene were twice as likely to cause venous thromboembolism as other low-dose oral contraceptives (Committee on Safety of Medicines 1995). The CSM went on to recommend that desogestrel and gestodene preparations should not be prescribed to women with risk factors for venous thromboembolism and that current users without such risk factors should only continue to take the newer pills if they did not tolerate older preparations and they were prepared to accept the excess risk.

Following this action by the CSM, drug regulatory authorities in Germany and Norway issued warnings about the excess risk and imposed prescribing restrictions (Carnall et al. 1995). The Federal Institute for Medical Drugs and Products in Germany ruled that women under the age of 30 years who were starting oral contraceptives for the first time were not to be prescribed contraceptives containing desogestrel or gestodene. It also asked manufacturers of these contraceptives to provide more detailed information about the risks of venous thromboembolism on the product information sheets provided to users. At the time, desogestrel and gestodene products were taken by about 30% of German oral contraceptive users. In Norway, only one product containing an implicated progestogen (desogestrel with 30μg ethinyloestradiol) was licensed for use and this was taken by about 35% of oral contraceptive users. The Norwegian Medicines Control Agency advised that this preparation should only be used by women who could not tolerate other pills and it was not to be prescribed to first-time users.

Authorities in several other countries chose not to issue immediate advice (Carnall et al. 1995). In the Netherlands, where about 63% of oral contraceptive users were taking desogestrel or gestodene pills, the Medicines Assessment College decided to await the publication of the relevant studies before making any decisions. A similar decision was made by the Canadian Federal Drugs Directorate. Gestodene preparations were not licensed for use in Canada and desogestrel products comprised about 12 – 15% of oral contraceptives used. The Food and Drug Administration in the USA concluded that the excess risk was insufficient to justify changing the 15% of pill users taking desogestrel

products to alternative preparations. Like Canada, the USA had never licensed gestodene products. In Australia, where about 5% of pill users took desogestrel or gestodene oral contraceptives, the Therapeutic Goods Administration undertook a review of prescribing warnings and cautions. The initial position of the European Union's Committee on Proprietary Medicinal Products was that until more data were available, it could not exclude the possibility that biases explained the apparent excess risk (Choo 1995). In New Zealand, where oral contraceptives containing desogestrel or gestodene were used by nearly 80% of pill users (Wilson 1999), the Ministry of Health's immediate response was to send a copy of the CSM statement to doctors and pharmacists and to recommend that women at high risk of venous thromboembolism should consider using other preparations (Paul 1996). A week later, the Ministry concluded that in fact no prescribing recommendations could be made until published data were available.

Responses to the CSM warning

The action taken by the CSM attracted considerable criticism, much of which echoed the concerns expressed following the early warning issued by the Committee on Safety of Drugs in December 1969. The similarity of responses was perhaps not surprising given that the CSM, like its predecessor, was forced to hold a press conference earlier than it had intended because of an unauthorised release of information to the media, and once again many doctors, pharmacists, and other health professionals, learned of the warning from the media or their patients before they received an official "Dear Doctor" letter (Craft 1995). Subsequently, there were anecdotal reports that doctors were deluged with telephone calls and visits from concerned patients (Davies et al. 1995; Graham et al. 1995; Hope 1995) and that some women stopped using oral contraceptives altogether (Armstrong et al. 1995; Ramsay 1996). Fears were also expressed that womens' confidence in the safety of oral contraceptives had been damaged by the publicity (Spitzer 1995; Allison 1996; Cramer 1996; Ketting 1996). Equally, other doctors reported that the "pill scare" had not caused as much trouble as they had anticipated — their patients had behaved with "common sense" (Seamark 1995) and were pleased to be offered the opportunity to change to products that carried a lower risk (Smith 1996).

More systematic examinations of the effects of the CSM announcement on oral contraceptive use and pregnancy trends offered a slightly confused picture. A review of prescription trends by the UK Prescription Pricing Authority revealed that, overall, the total number of women taking oral contraceptives remained stable, although the proportion of oral contraceptive users taking desogestrel or gestodene preparations fell from 55% in September 1995 to 12% by February 1996 (Ferguson and Jenkins 1996). Similar utilisation patterns were observed for various sub-groups of women (Martin et al. 1997; Flett et al. 1998; Jick et al. 1998a). The pregnancy data were less consistent. While no increases in abortions or births were found in some groups (Flett et al. 1998; Jick et al. 1998a), in others the abortion rates appeared to have risen following the CSM announcement (Child et al. 1996; Ramsay 1996). In the UK, overall, the Office for National Statistics estimated that an excess 30,000 conceptions occurred between October 1995 and June 1996 (Wood et al. 1997). The abortion rates in Norway were also said to have climbed following the warning issued by the regulatory authority in that country (Iversen and Tore Nilsen 1996; Skjeldestad 1997). However, some of these accounts were criticised for failing to take longer trends in unwanted pregnancies into account (Vandenbroucke et al. 2000).

In New Zealand, an examination of oral contraceptive prescription data for the period January 1995 to March 1998 revealed that the proportion of women of child-bearing age who were using oral contraceptives did not change following the CSM warning or the release of prescribing advice by the New Zealand Ministry of Health (Wilson 1999). It was also apparent that most women continued to take their usual oral contraceptive. In October 1995, desogestrel and gestodene contraceptives were taken by about 79% of pill users; this proportion dropped only slightly to 74% immediately after the CSM announcement and thereafter declined gradually to 62% by March 1998. Apart from a small increase in abortions in women aged 15 – 19 years in March 1996, there was no indication that the CSM or Ministry of Health advice had any impact on overall or age-specific abortion rates in New Zealand (Wilson 1999).

The Transnational study investigators also expressed dismay over the CSM's actions. In a letter published in the BMJ on 28 October 1995, the principal investigator reported that once the analyses were completed his group had shared their findings with the UK Medicines Control Agency, a subcommittee of the CSM, and German regulatory

authorities in confidence (Spitzer 1995). Without further consultation, a few days later, the CSM made its announcement. Such action, claimed the principal investigator, was hasty and not warranted by the "modest" relative risks and "very low" attributable risks. Moreover, he and his colleagues believed that "five unavoidable biases might be driving the risks up spuriously."

The CSM also drew immediate criticism from other quarters for issuing a warning before the data on which it was based were published (Carnall 1995; Editorial 1995; Guillebaud 1995a; Simpson and Elstein 1996). It was also suggested that the CSM acted beyond its legal authority by issuing advice (Watt 1995a). The Chairman of the CSM responded by saying that much of the work of the Committee involved assessing data which were unpublished and, moreover, the CSM would be "failing in its duty....if it did not communicate important drug safety information promptly" (Rawlins 1995). Furthermore, he considered that the CSM had not acted with undue haste since it had been aware of the results of the WHO study since July 1995.

Concerns were also expressed that the CSM action had compromised ongoing research into oral contraceptives and myocardial infarction and stroke (Davis et al. 1995; MacRae and Kay 1995; Spitzer 1995; Wynn et al. 1995; Simpson and Elstein 1996) and that the continued involvement of pharmaceutical companies in contraceptive research and development might have been jeopardised (Wynn et al. 1995; Cramer 1996).

Representatives of the company which manufactured an oral contraceptive containing norgestimate, were quick to emphasise that their product was not implicated in the CSM warning (Donnelly 1995; Donnelly 1996a; Donnelly 1996b). In fact, it was not that norgestimate contraceptives had been shown to be safer than desogestrel and gestodene products — it was simply that the key studies provided insufficient data to allow an assessment of venous thromboembolism risk (Walker 1998).

3.2.4 The key studies

Two months after the CSM announcement, on 16 December 1995, the WHO, GPRD, and Leiden studies were published in the Lancet (Bloemenkamp et al. 1995; Jick et al. 1995; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995b; World Health Organization Collaborative Study

of Cardiovascular Disease and Steroid Hormone Contraception 1995c); the Transnational study appeared the following month in the BMJ (Spitzer et al. 1996). The details of these studies are shown in Table 3.3.

Table 3.3 Key studies which examined the association between oral contraceptive use and venous thromboembolism by progestogen type

Reference	Study design	Cases	Controls	Exposure information	Adjustment factors	Results
(World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995a; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995b) (WHO study)	Hospital-based case-control study in 21 centres in 17 countries in Africa, Asia, Europe, and Latin America. 2 groups for analyses: Europe and "developing countries" (Africa, Asia, Latin America combined). Study period: February 1989 – January 1993.	Ascertainment Monitoring system in each centre identified cases with DVT and / or PE, classified as "definite", "probable", "possible", or "other" based on signs, symptoms, and results of investigations. Certainty of diagnosis 58% definite, 28% probable, 7% possible, 8% other. Index date Date of VTE event. Inclusion criteria Women aged 20 – 44 years (15 – 49 years in 3 centres). Exclusion criteria Cases classified as other; deaths < 24 hrs after admission; previous history DVT, PE, CVA, MI; natural or surgical menopause; pregnancy, severe trauma, surgery, or illness requiring medical attention and causing prolonged bed rest < 6 weeks before index date. Total included n = 1143	Selection For each case, ≤ 3 controls selected from women admitted to same hospital with 1 of 27 diagnoses unrelated to OC use, < 2 weeks before and < 4 months after case. Matching factors Study centre, age (5-year bands). Index date Date of admission. Inclusion / exclusion criteria As for cases. Total included n = 2998	Cases and controls interviewed in hospital using standardised questionnaire – demographic data, medical and reproductive history, contraceptive use, other medications, weight, height, smoking status, alcohol use, family history CVA or MI. Shown samples or pictures of locally available OCs. Current use of OC Use at any time ≤ 3 months before index date. *1st generation OC:* EE with ethynodiol diacetate, lynoestrenol, norethisterone, norethisterone acetate, or norethynodrel. *2nd generation OC*: EE with norgestrel, LNG, or norgestrienone. *3rd generation OC:* EE with DSG, GSD, or NGM. *Other OC:* EE with CPA. Reference category Non-users (never and past users combined).	Explored effect of large number of potential confounders in sequential manner, retained in model if resulted in ≥ 5% change in OR. Only identifiable confounder in Europe was PIH. No confounders in developing countries.	**Europe, adjusted matched OR (95% CI) for current use < 50µg EE OC** ***Non-users as reference*** Any OC: 4.24 (3.07 – 5.87) 1st generation OC: 3.37 (1.44 – 7.93) 2nd generation OC: 3.61 (2.53 – 5.13) 3rd generation OC: 7.36 (4.20 – 12.90) Other OC: 15.70 (3.90 – 63.15) **Developing countries, adjusted matched OR (95% CI) for current use < 50µg EE OC** ***Non-users as reference*** Any OC: 3.02 (2.28 – 4.00)

Reference	Study design	Cases	Controls	Exposure information	Adjustment factors	Results
(World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995c) (WHO study)	Hospital-based case-control study, confined to centres in which there were any cases or controls who were current users of OCs containing DSG or GSD (10 centres in 9 countries). GP-based controls also selected for cases in 1 centre (Oxford). Study period: February 1989 – January 1993.	Ascertainment Methods as above. Certainty of diagnosis 42% definite, 42% probable, 9% possible, 7% unspecified. Index date Date of VTE event. Inclusion criteria Women aged 20 – 44 years (15 – 49 years in 3 centres). Exclusion criteria As above. Also users of OCs containing > 35µg EE, women for whom OC type unknown (n=3) or no controls identified (n=3). Total included n = 769	Selection Hospital-based controls as above. Also ≤ 2 controls per case also randomly selected from age-sex register of same GP as case (in Oxford region). Matching factors Study centre, age (5-year bands), GP (GP-based controls). Index date Date of admission for hospital-based controls. Not explicitly stated for GP-based controls. Inclusion / exclusion criteria As for cases. Total included n = 1979 (hospital) plus 246 (GP).	Cases and controls interviewed in hospital or at home (community-based controls) using standardised questionnaire as above. Current use of OC Use at any time ≤ 3 months before index date. Reference categories 1. Non-users (never and past users combined). 2. Current users of OCs containing < 35µg EE with LNG (1 case and 2 controls who were users of NGM, reclassified with LNG group).	Explored effect of large number of potential confounders in sequential manner, retained in model if resulted in ≥ 5% change in OR. BMI and alcohol consumption only confounders in all centres analyses.	**All centres (hospital controls) adjusted matched OR (95% CI) for current use < 35µg EE OC** ***Non-users as reference*** Any OC: 4.1 (3.2 – 5.2) LNG OC: 3.4 (2.5 – 4.7) DSG or GSD OC: 9.4 (5.6 – 15.6) CPA OC: 14.9 (3.7 – 59.4)* ***LNG OC users as reference*** DSG OC: 2.4 (1.3 – 4.6) GSD OC: 3.1 (1.6 – 5.9) DSG or GSD OC: 2.7 (1.6 – 4.6) CPA OC: 5.1 (1.3 – 20.3)* **Rate idiopathic VTE (Oxford region) per 100,000 woman-years** Users DSG or GSD OC: 21.3 Users LNG OC: 10.3 Non-users: 3.9

Reference	Study design	Cases	Controls	Exposure information	Adjustment factors	Results
(Jick et al. 1995) (GPRD study)	Study population Based on UK GPRD. Women aged < 40 years who received ≥ 1 prescriptions for OCs containing ≤ 35µg EE with LNG, DSG, or GSD between January 1991 and November 1994. Excluded women with previous DVT, PE, CVA, MI, cancer, epilepsy, diabetes, treated hypertension, hyperlipidaemia, or cystic fibrosis. ***Study 1*** Cohort study of idiopathic CV death. ***Study 2*** Nested case-control and cohort studies of idiopathic non-fatal VTE.	Ascertainment ***Study 1*** Reviewed electronic records of 470 GPs to identify women whose cause of death was recorded as PE, CVA, MI, cardiac arrest, or "sudden death". Examined death certificates and necropsy reports. ***Study 2*** Reviewed electronic records of 365 GPs to identify women who were admitted to hospital with objectively diagnosed DVT and / or PE and anticoagulated. Examined hospital referral and discharge letters. Classified VTE as "confirmed" or "possible" according to results of investigations. Certainty of diagnosis ***Study 2, cohort analysis*** 64% confirmed, 36% possible. Index date Unclear whether date of admission or date of onset of symptoms. Additional exclusion criteria ***Study 1*** Trauma or surgery < 3 months before death, cerebral haemorrhage secondary to congenital cerebrovascular malformation. ***Study 2*** Women not exposed to a study OC on index date; fatal events; pregnancy, trauma or surgery < 3 months before index date. Total included ***Study 1*** 15 deaths ***Study 2*** 80 non-fatal cases (cohort analysis), 75 non-fatal cases (case-control analysis).	Selection For each case in case-control analysis of study 2, 4 controls exposed to a study OC on the index date were randomly selected from the study population. Matching factors GP, age (2-year bands, 5-year bands for 15%). Index date Index date of case. Exclusion criteria As for cases in study 2. Total included n = 300	***Both studies*** Details of OC exposure and other data abstracted from electronic records. ***Study 2*** Standardised questionnaire sent to general practitioners. Current use of OC Use on index date. Reference category Current users of OCs containing LNG with ≤ 35µg EE.	***Study 1*** Age (< 30, 30 – 39 years) and calendar time. ***Study 2*** *Nested case-control analysis* BMI, smoking. *Cohort analysis* Age (< 30, 30 – 39 years) and calendar time.	***Study 1*** **Adjusted RR (95% CI) for current use < 35µg EE OC** ***LNG OC users as reference*** DSG OC: 0.4 (0.1 – 2.1) GSD OC: 1.4 (0.5 – 4.5) **Crude CV mortality rate per 100,000 woman-years** Users DSG OC: 1.5 (0.4 – 5.4) Users GSD OC: 4.8 (2.0 – 11.1) Users LNG OC: 4.3 (2.2 – 8.6) ***Study 2*** **(a) Nested case-control analysis** **Adjusted matched OR (95% CI) for current use < 35µg EE OC** ***LNG OC users as reference*** DSG OC: 2.2 (1.1 – 4.4) GSD OC: 2.1 (1.0 – 4.4) **(b) Cohort analysis** **Adjusted RR (95% CI) for current use < 35µg EE OC** ***LNG OC users as reference*** DSG OC: 1.9 (1.1 – 3.2) GSD OC: 1.8 (1.0 – 3.2) **Crude rate idiopathic VTE per 100,000 woman-years** Users DSG OC: 29.3 (20.5 – 41.9) Users GSD OC: 28.1 (18.5 – 42.5) Users LNG OC: 16.1 (10.7 – 24.1) Past users: 3.8 (1.6 – 9.0)

Reference	Study design	Cases	Controls	Exposure information	Adjustment factors	Results
(Vandenbroucke et al. 1994; Bloemenkamp et al. 1995) (Leiden study)	Reanalysis of Leiden Thrombophilia Study, a population-based case-control study of consecutive men and women aged < 70 years with a 1st diagnosis of DVT between January 1988 and December 1992. Patients with known malignancy excluded.	Ascertainment Examined files of anticoagulation clinics in 3 regions in the Netherlands to identify cases with objectively diagnosed DVT. Certainty of diagnosis 100% definite. Index date Date of DVT. Inclusion criteria (reanalysis) Pre-menopausal women aged 15 – 49 years. Exclusion criteria (reanalysis) Pregnant < 30 days before index date, use of injectable progestogens, malignancy. Also users of OCs for whom insufficient numbers of cases and controls exposed (including GSD, CPA OCs) and women for whom OC type unknown. Total included (reanalysis) n = 126	Selection Each case was asked to find a friend or acquaintance of the same sex and age, who was not a biological relative, had no history of VTE or malignancy, and did not use warfarin, to serve as a control. Cases who were unable to find a suitable control were matched with partners of other cases. Matching factors Age. Index date Index date of case. Inclusion / exclusion criteria (reanalysis) As for cases. Total included (reanalysis) n = 159	Cases and controls both interviewed 6 – 19 months after index date (1990 – 1993) about risk factors for DVT, including OC use and a history of VTE in ≥ 1 parent or sibling. Physical examination undertaken and blood collected for coagulation factor and FVL analysis. Current use of OC Use ≤ 1 month before index date. Reference categories 1. Non-users (never and past users combined). 2. Current users of OCs containing LNG with 30µg EE. 3. Current users of any study OC (other than DSG with 30µg EE).	Undertook unmatched analysis because one or other of many case-control pairs were excluded because of additional inclusion and exclusion criteria in reanalysis. Adjusted for age as continuous variable.	**All women, adjusted unmatched OR (95% CI) for current use OC** ***Non-users as reference*** LNG OC: 3.8 (1.7 – 8.4) DSG OC: 8.7 (3.9 – 19.3) ***LNG OC as reference*** DSG OC: 2.2 (0.9 – 5.4) ***Any study OC as reference*** DSG OC: 2.5 (1.2 – 5.2) **Non-carriers of FVL mutation, adjusted unmatched OR (95% CI) for current use OC** ***Non-users as reference*** DSG OC: 9.2 (3.9 – 21.4) **Carriers of FVL mutation, adjusted unmatched OR (95% CI) for current use OC** ***Non-users as reference*** DSG OC: 6.0 (1.9 – 19.0) 8-fold increased risk of DVT in carriers of FVL mutation, hence risk of DVT in carriers using DSG OCs increased almost 50-fold compared with non-carrier non-users.

Reference	Study design	Cases	Controls	Exposure information	Adjustment factors	Results
(Spitzer et al. 1993; Spitzer et al. 1996; Lewis et al. 1996a) (Transnational study)	Hospital-based case-control study in 16 centres in UK, Germany, Austria, France, Switzerland. Primarily presented results from 10 centres in UK and Germany. Study period UK and Germany: August 1993 – Oct 1995. Study period Austria, France, Switzerland: late 1994 – October 1995.	Ascertainment Monitoring system in each centre identified cases with DVT and / or PE, classified as "definite", "probable", "possible", or "incorrect" by local committee of experts. Certainty of diagnosis Not stated. Index date Date of diagnosis. Inclusion criteria Women aged 16 – 44 years resident within specified geographical areas. Exclusion criteria Previous history DVT, PE, CVA, MI; hysterectomy; pregnancy, surgery, trauma requiring GA or causing immobility < 6 weeks before index date. Total included n = 471 (UK, Germany).	Selection For each case, ≥ 3 controls: ≥ 1 control from women admitted to same hospital as case with diagnosis unrelated to OC use (same as for WHO study) < 2 weeks before and < 4 months after case. ≥ 1 control from community - same GP as case (UK) or neighbourhood population lists (Germany), interviewed < 4 months after interview with case. Matching factors Hospital or community setting, age (5-year age bands). Index date Date of admission (hospital-based) or interview (community-based). Inclusion / exclusion criteria As for cases. Total included (UK, Germany) n = 789 (hospital) plus 983 (community).	Interviews based on standardised questionnaire used in WHO study. Validated type of OCs used by examining pill packets of sample of women. Current use of OC Use at any time ≤ 3 months before index date. *1st generation OCs:* 50µg EE with any progestogen. *2nd generation OCs:* ≤ 35µg EE with progestogen other than DSG or GSD (OCs with NGM and CPA classified as 2nd generation). *3rd generation OCs:* ≤ 30µg EE with DSG or GSD. Reference categories 1. Non-users (never and past users combined). 2. Users of 2nd generation OCs.	Undertook unmatched (unexplained) analyses and adjusted for study centre, age, smoking, alcohol use, BMI, and duration of past OC use. Also undertook matched analyses, but key results reported were from the unmatched analyses.	**Germany and UK, adjusted unmatched OR (95% CI) for current OC use** ***Non-users as reference*** Any OC: 4.0 (3.1 – 5.3) 1st generation OC: 5.7 (3.4 – 9.4) 2nd generation OC: 3.2 (2.3 – 4.3) 3rd generation OC: 4.8 (3.4 – 6.7) ***2nd generation OC users as reference*** 3rd generation OC: 1.5 (1.1 – 2.1) DSG OC: 1.5 (1.1 – 2.2) GSD OC: 1.5 (1.0 – 2.2) **5 countries combined, adjusted unmatched OR (95% CI) for current OC use** ***2nd generation OC users as reference*** 3rd generation OC: 1.7 (1.3 – 2.4) **Germany and UK, adjusted matched OR (95% CI) for current OC use** ***2nd generation OCs as reference*** 3rd generation OC: 1.6 (1.2 – 2.2)

* Unadjusted matched analysis.

Abbreviations used in the table BMI: body mass index, CPA: cyproterone acetate, CV: cardiovascular, CVA: stroke, DSG: desogestrel, DVT: deep vein thrombosis, EE: ethinyloestradiol, FVL: factor V Leiden mutation, GP: general practice, GSD: gestodene, HRT: hormone replacement therapy, LNG: levonorgestrel, MI: myocardial infarction, NGM: norgestimate, OC: oral contraceptive, OR: odds ratio, PE: pulmonary embolism, PIH: pregnancy-induced hypertension, RR: relative risk, VTE: venous thromboembolism.

3.2.5 Doubts about the validity and importance of the findings of the key studies

In the immediate discussions that followed the publication of the key studies, it soon became apparent that while some commentators felt the findings reflected a true excess risk of venous thromboembolism in users of desogestrel and gestodene oral contraceptives (Weiss 1995; McPherson 1996), others were doubtful that these preparations carried a higher risk than older preparations (Watt 1995b; Cramer 1996; Johannisson and The International Committee for Research in Reproduction 1996; Rosenberg et al. 1996; Lidegaard and Milsom 1996a). At issue, was the size of the relative risk estimates which were said to be "so small in epidemiological terms that modest bias could account for an effect of this size" (Rosenberg et al. 1996).

In the months following the CSM announcement and the publication of the key studies, various biases were proposed that might at least partially explain the observed association (Watt 1995b; Guillebaud 1995b; Cramer 1996; Johannisson and The International Committee for Research in Reproduction 1996; Rosenberg et al. 1996; Westhoff 1996; Farmer and Lawrenson 1996a; Lidegaard and Milsom 1996a); many of these were proposed by the Transnational investigators (Davis et al. 1995; Spitzer 1995) and associates (MacRae and Kay 1995), representatives of pharmaceutical companies (Reijnen and Atsma 1995; Kaper 1996), and by participants at meetings funded by oral contraceptive manufacturers (Rosenberg et al. 1996; Cohen 1996a). At a press conference held a few days after the CSM announcement (for which he flew from Canada to London), the principal investigator of the Transnational study referred to at least three potential biases: confounding by indication, referral bias, and the switching of high-risk women into the pool of third generation pill users (Carnall 1995).

For some commentators the consistency of the results of the published studies, which involved different methods and different study populations, was not convincing evidence that the difference in risk between the newer and older oral contraceptives was real; it was suggested that all of the studies might have been subject to the same types of bias (Westhoff 1996). Furthermore, it was argued that the observation that the highest estimates for desogestrel and cyproterone acetate products were found for the formulations that contained the lowest doses of oestrogen ran contrary to the generally accepted belief that contraceptives with higher oestrogen doses carried higher risks of venous thromboembolism, and hence these findings were interpreted as evidence of bias

(Westhoff 1996). Similarly the apparent fall in absolute risk associated with older preparations was also thought to reflect the influence of bias (Kaper 1996). Residual confounding was also raised as a possible alternative explanation for the association (MacRae and Kay 1995). However, the CSM reiterated that neither chance, bias, or confounding could explain the overall findings of the key studies (Rawlins 1995).

Other arguments advanced against a causal relationship were that there had been no increase in the incidence of venous thromboembolism among women of child-bearing age since the introduction of desogestrel and gestodene contraceptives (Lidegaard and Milsom 1996a), and there was no biologically plausible explanation for a higher risk in users of such products — particularly since they had been shown in the laboratory to have less unfavourable effects on haematological and biochemical parameters than older preparations (Johannisson and The International Committee for Research in Reproduction 1996).

It was also maintained that even if the difference in risk between desogestrel and gestodene preparations and older products was real, the attributable risk and public health impact were negligible (Spitzer 1995). In fact, one commentator (Guillebaud 1995a) made the absolute risks appear even smaller by misrepresenting annual incidence (Rawlins 1995). Furthermore, it was argued that the incidence of pregnancy-related venous thromboembolism was much higher than the risk in oral contraceptive users (Guillebaud 1995a). Finally, some commentators asserted that any increased risk of venous thromboembolism associated with desogestrel and gestodene contraceptives might be outweighed by other benefits conferred by these products (MacRae and Kay 1995; Guillebaud 1995a).

In the following sections, these issues of internal validity, biological plausibility, the importance of any difference in risk, and other possible benefits of desogestrel and gestodene contraceptives will be considered in more detail.

3.2.6 Consideration of possible non-causal explanations for the association

Prescription bias or confounding by indication

Proponents of this hypothesis argued that because desogestrel and gestodene contraceptives were marketed as having a safer cardiovascular safety profile than older

products, doctors preferentially prescribed these pills to women who were at higher risk of venous thromboembolism and hence the apparent excess risk of venous thromboembolic events was due to the underlying characteristics of the users rather than the products themselves (Johannisson and The International Committee for Research in Reproduction 1996; Cohen 1996a; Lidegaard and Milsom 1996a). Curiously, the Transnational investigators, who stated in their original publication that the "existence of prescribing bias is not corroborated in our data" (Spitzer et al. 1996), were also strong advocates of this theory (MacRae and Kay 1995; Lewis et al. 1996b; Spitzer 1997).

Arguments in support of this hypothesis ran as follows. During the periods under investigation in the WHO, GPRD, Leiden, and Transnational studies, family planning experts and prescriber information sources such as the British National Formulary had recommended that desogestrel and gestodene pills be prescribed for "high-risk" women (Spitzer 1997). Moreover, several surveys were said to provide evidence that selective prescribing had occurred (Heinemann et al. 1996; Jamin and de Mouzon 1996; van Lunsen 1996a; Lidegaard 1997). It was also asserted that the key studies had too few cases to have allowed a full exploration of the effects of a large number of potential confounders (Farmer and Lawrenson 1996a). A final argument related to the findings of inverse dose-response relationships for ethinyloestradiol in oral contraceptives containing desogestrel (Jick et al. 1995; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995c) and cyproterone acetate (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995b; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995c). Such findings were thought to be biologically implausible and thus were evidence of confounding by indication (Westhoff 1996; Lewis et al. 1996b; Lidegaard and Milsom 1996b; Spitzer 1997; Farmer et al. 1997a; Cohen 1999).

The question "is it the drug or the characteristics of the people who take the drug which is responsible for an apparent adverse reaction?" is a legitimate enquiry in studies of drug safety. However, in this instance, the confounding by indication hypothesis did not stand up to quantitative scrutiny (Farley et al. 1996; Helmerhorst et al. 1997; Vandenbroucke et al. 1997a; Walker 1998; Farley et al. 1999; Walker 1999). To

account for a doubling of risk in users of desogestrel or gestodene contraceptives, when compared with users of older pills, a confounding factor would have to be both an important risk factor for venous thromboembolism and be strongly associated with the decision to prescribe a third generation contraceptive (Walker 1998). It was estimated, for example, that if the suspected confounding factor was present in 20% of women using desogestrel or gestodene pills and 5% of the other users, that factor would need to be associated with an 11-fold increased risk of venous thromboembolism (Walker 1999). A risk factor with such an effect was difficult to imagine. All of the key studies had excluded women with a previous history of venous thromboembolism and several other major risk factors (such as pregnancy, bed rest, surgery, or trauma), the effects of age were accounted for, and potential confounding by a large number of factors was explored (Farley et al. 1996). Risk factors such as obesity were adjusted for in the analyses — although, other than controlling for age, adjustment for potential confounders made no difference to the relative risk estimates (Walker 1998). The presence of inherited genetic mutations which increase the risk of venous thromboembolism were unlikely to have influenced prescribing decisions as they were not widely known about at the time of the studies and some had only recently been discovered (Vandenbroucke et al. 1997a). Information about a family history of venous thromboembolism was not collected in the WHO, GPRD, and Transnational studies, and thus potential confounding by this factor could not be explored. However, a stratified analysis in the Leiden study showed that a two-fold difference in risk between users of desogestrel and levonorgestrel pills was present in women both with, and without, a family history (Bloemenkamp et al. 1995). Similarly, in an analysis confined to women without hereditary thrombophilia in a Danish case-control study, the relative risk estimate for users of desogestrel and gestodene preparations compared with non-users was higher (20.9 [95% CI 3.1 – 141.3]) than the estimate for older pills (7.1 [95%CI 2.0 – 25.2]) (Andersen et al. 1998).

In relation to other factors that might have been implicated in possible confounding by indication, it was pointed out that contemporary textbooks offered "very few clinical risk factors that predict the occurrence of a first venous thrombosis in healthy young persons" (Vandenbroucke et al. 1997a). Indeed, some commentators suggested that any differential prescribing was more likely to be related to risk factors for arterial, rather than venous, thrombosis (Farley et al. 1999). Moreover it was thought to be "extremely

unlikely that factors strong enough to affect physicians' prescribing choices would fail uniformly to have been recognized and adjusted for in all studies based ultimately on medical records" (Walker 1998).

Several concerns were also expressed about the surveys of prescribing behaviour which were claimed to support the confounding by indication hypothesis. In a small German drug utilisation study conducted in December 1995, doctors reported that they would choose to prescribe desogestrel and gestodene contraceptives to women with risk factors for venous thromboembolism (Heinemann et al. 1996). However, an examination of those doctors' records revealed only a small trend towards the asserted practice. Doctors in a UK survey also expressed a preference for prescribing desogestrel and gestodene contraceptives to women with venous thrombotic risk factors, however a review of their clinical records found no evidence of any selective prescribing (Dunn et al. 1998). Such findings led a commentator to warn that surveys of doctors' attitudes might be unreliable sources of information about actual prescribing behaviour and thus doubt was cast upon alleged selective prescribing practices in France, Sweden, and the Netherlands (Walker 1999).

Moreover, it appeared that any selective prescribing might have had minimal influence on estimates of excess risk associated with the use of desogestrel and gestodene pills. For example, in a Danish study that sought to quantify the possible impact of confounding by indication, it was reported that selective prescribing might account for about 15% (at most) of the excess risk (Lidegaard 1997). The information linking prescription choices with risk factors was obtained from the control series selected for a case-control study of stroke (Lidegaard and Kreiner 1998), and most of the reported selective prescribing of desogestrel and gestodene contraceptives was to women with a family history of venous thromboembolism (Lidegaard 1997). This same group of women was also used as the control series in a later case-control study of venous thromboembolism (Lidegaard et al. 1998), but as one commentator has noted, it appears that a family history did not act as a confounder of the association between pill type and the risk of venous thromboembolism in that study once adjustments were made for age (Walker 1998).

Finally, it was suggested that the unexpected inverse ethinyloestradiol dose-response observed for oral contraceptives containing desogestrel might reflect a combination of a starter effect and an effect of desogestrel (Vandenbroucke et al. 1997b).

First-time user, healthy user, attrition of susceptibles, and recency of introduction biases

In effect, these biases all referred to the same phenomenon (Vandenbroucke et al. 1997a). Central to this hypothesis, was the suggestion that the risk of venous thromboembolism among oral contraceptive users is highest during the first year of use (Reijnen and Atsma 1995). Therefore, it was argued, duration of use must be taken into account when making risk comparisons between contraceptives containing desogestrel or gestodene and older preparations (Reijnen and Atsma 1995). This was because women starting on oral contraceptives for the first time were more likely to be prescribed the newest products on the market (MacRae and Kay 1995), and hence the cohort of desogestrel and gestodene contraceptive users would include a disproportionate number of women who were first-time and short-term users. Moreover, it was likely that women who had been taking oral contraceptives for some time would be users of older products and would comprise a cohort of "healthy users", since users at high risk for thrombosis would already have suffered such an event or been identified as carrying a substantial risk and thus would have been removed from the cohort (Watt 1995b). In addition, it was suggested that the cohort of users of older products was being "depleted of" and the cohort of third generation pill users "enhanced with" high-risk women (Guillebaud 1995b). The overall impact of such factors would be that users of desogestrel and gestodene contraceptives were, independent of pill type, at higher risk of venous thromboembolism than the group of women taking older pills — hence, the apparent excess risk of venous thromboembolism in users of desogestrel and gestodene pills was not due to the products themselves, but rather it was because dissimilar cohorts of women were being compared (MacRae and Kay 1995; Reijnen and Atsma 1995; Watt 1995b; Guillebaud 1995b; Cramer 1996; Johannisson and The International Committee for Research in Reproduction 1996; Rosenberg et al. 1996; Cohen 1996a; Lidegaard and Milsom 1996a; Farmer and Lawrenson 1996b; Lewis et al. 1996b; Spitzer 1997).

Advocates of this hypothesis pointed out that the incidence of venous thromboembolism in desogestrel and gestodene pill users was no higher than the rates reported for older

products some years before — in fact, the apparent excess risk was because the incidence among users of older products was appreciably lower than in previous reports (Farmer and Lawrenson 1996a; Lidegaard and Milsom 1996a). This, they argued, was evidence of a cohort effect because it was implausible that the risk had actually declined over time. However, this argument was criticised on the basis that it was not valid to compare incidence rates from different periods because the age distribution of users and the methods used to diagnose venous thromboembolism had changed substantially (Farley et al. 1996; Vandenbroucke et al. 1997a).

Other support for the hypothesis was said to be provided by four reanalyses of the Transnational study, as well as some new research. In the first of the Transnational reanalyses, the risks of venous thromboembolism for various formulations containing desogestrel, gestodene, and norgestimate were compared with low-dose levonorgestrel products (Lewis et al. 1996b). A linear trend of increasing odds ratios with decreasing time since the products were introduced onto the market was said to confirm the presence of bias. However, the investigators were criticised for restricting this analysis to women aged 25 – 44 years (Weiss 1997; Vandenbroucke et al. 1997c). Analyses including the full dataset of women aged 16 – 44 years showed no such trend (Weiss 1997) and, in fact, an opposite trend was shown for women aged 16 – 24 years (Vandenbroucke et al. 1997c). Moreover, in the latter group of women, among whom most new users would be expected, desogestrel, gestodene, and norgestimate pills carried a higher risk of venous thromboembolism than levonorgestrel preparations (Vandenbroucke et al. 1997c). The Transnational investigators justified their sub-analysis by claiming that it was necessary to study women who had been using oral contraceptives long enough for "attrition of susceptibles" to have occurred (Lewis and Spitzer 1997). This reasoning was later called into question by the results of the second reanalysis of the Transnational study (Suissa et al. 1997). In that analysis, the initial increase and then decline in risk in new users relative to never users was shown to plateau after about two years— leading one commentator to observe that if this decline was "attributable to depletion of susceptibles, the interval necessary to create an established (depleted) user pool would be only a few years, and the critics of the exclusion of younger women from the reanalysis would be correct" (Walker 1998).

In the second reanalysis of the Transnational study, the risk of venous thromboembolism in never users was compared with two groups of first-time users of oral contraceptives: those taking desogestrel or gestodene preparations and those using levonorgestrel or norgestimate products (Suissa et al. 1997). Relative risks estimated for different durations of current use (less than one year, one to two years, three to five years, and more than five years), showed that for both groups of users the risk was greatest during the first year of use. When a quadratic spline model was used to compare the risks as a function of duration of use in the two groups of first-time users relative to never users, no difference between the two groups of products was found. However, the WHO investigators suggested that this was an artefact of the constraints placed on the model, which did not allow for a rapid increase in risk of venous thromboembolism following the initiation of oral contraceptive use (Farley et al. 1998a). A reanalysis of the WHO data using an unconstrained spline model showed a difference between first-time users of desogestrel or gestodene preparations and first-time users of levonorgestrel pills.

The findings of the second Transnational reanalysis were also at variance with the results of a stratified analysis in the WHO study which showed an excess risk of venous thromboembolism in first-time users of oral contraceptives containing desogestrel and gestodene, when compared with first-time users of levonorgestrel (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995c). Moreover an excess risk associated with desogestrel and gestodene pills was present regardless of duration of use (Poulter et al. 1996a). Similar findings were reported by the GPRD (Jick et al. 1995; Jick et al. 1996a) and Leiden investigators (Bloemenkamp et al. 1995; Vandenbroucke et al. 1996a) and, indeed, in the first report of Transnational study (Spitzer et al. 1996). A later cohort study in the Netherlands, which linked prescription data with hospital discharges, also showed that first-time users of oral contraceptives who took desogestrel and gestodene preparations had a higher risk of venous thromboembolism than women who used levonorgestrel products; the relative risk was 3.5 (95% CI 1.4 – 8.8) (Herings et al. 1999).

Undeterred by evidence to the contrary, the Transnational investigators continued to assert that a healthy user effect could explain the differential risk associated with desogestrel and gestodene oral contraceptives. Hence, they undertook a third reanalysis

of their data, this time using a Cox proportional hazards model to take into account the full duration of oral contraceptive use (Lewis et al. 1999). The excess risk associated with desogestrel and gestodene pills relative to low-dose pills containing other progestogens disappeared. But this approach, of analysing data from a case-control study as if they were derived from a cohort study, was severely criticised (Farley et al. 1999).

In a fourth reanalysis, the Transnational investigators invoked the possibility that failure to take patterns of oral contraceptive use fully into account had led to biased estimates in the previous studies (Suissa et al. 2000). Oral contraceptive users were classified as first-time users, repeaters (women who had had interrupted episodes of use of oral contraceptives from the same generation as they were currently using), or switchers (women who had switched to desogestrel or gestodene pills after using levonorgestrel or norgestimate preparations, or vice versa). In sub-analyses involving repeaters and switchers only, comparisons between desogestrel and gestodene preparations and those containing levonorgestrel and norgestimate were adjusted for duration of current use, length of interruption, and duration of previous use. No excess risk was found for desogestrel and gestodene products.

A group of Danish investigators professed to have demonstrated that bias explained at least some of the apparent excess risk associated with desogestrel and gestodene contraceptives. In a case-control study, an elevated risk of venous thromboembolism associated with desogestrel and gestodene preparations compared with levonorgestrel and norgestimate products (odds ratio 1.70 [95% CI 1.05 – 3.06]) was attenuated after adjusting for duration of use (odds ratio 1.44 [95% CI 0.83 – 2.50]) (Lidegaard et al. 1998). However, the treatment of duration of use as a confounding factor, rather than an exposure variable, was criticised (Walker 1998). Moreover, it was argued that it was not possible to reliably separate out the effects of duration of use and progestogen type because almost all of the short-term users were taking desogestrel or gestodene contraceptives. A final criticism was that the controls were originally selected as age-matched controls for a case-control study of stroke, and the cases were required to recall oral contraceptive use in the more distant past than were the controls.

In spite of the repeated efforts to show that the bias, variously referred to as first-time user, healthy user, attrition of susceptibles, and recency of introduction bias, explained the excess risk associated with the use of desogestrel and gestodene contraceptives, many commentators remained unconvinced (Farley et al. 1996; Helmerhorst et al. 1997; Vandenbroucke et al. 1997c; Walker 1998; Farley et al. 1999; O'Brien 1999; Walker 1999; Hannaford 2000). In addition to the points discussed above, they offered several other arguments against such a hypothesis. First, a "recency of introduction" bias had not been found in earlier studies (Walker 1998) — in fact, new products had been found to carry lower risks of venous thromboembolism (Inman et al. 1970; Böttiger et al. 1980; Meade et al. 1980; Gerstman et al. 1991).

Second, since "established users" of older pills comprised only a small proportion of the user group in the Transnational study, such women would have needed to have the same risk of venous thromboembolism as non-users to produce a spurious doubling of risk in users of desogestrel and gestodene contraceptives (Walker 1998). This proposition — that all high-risk women are eventually removed from the group of oral contraceptive users — was contrary to the observation that current use of any type of oral contraceptive conferred a higher risk of venous thromboembolism than non-use (Walker 1998). Moreover, the attrition of susceptibles argument also required that the small number of women who were removed from the pool of users carried a considerably elevated risk of venous thromboembolism (Vandenbroucke et al. 1997a).

Third, the suggestion that the pool of users of desogestrel and gestodene pills was somehow "enriched" with women at higher risk for venous thromboembolism who had switched from using older preparations (thus "depleting" that pool of users) was rejected as an explanation for the results of the key studies (Vandenbroucke et al. 1997a). As, with the "depletion of susceptibles" proposition, the "switching" hypothesis also required that the women who were changing to desogestrel and gestodene formulations carried a much higher risk of venous thromboembolism. However, the main reasons given for switching from older preparations to desogestrel and gestodene contraceptives in one study were side effects such as poor cycle control and acne (Farmer et al. 1996), which are unrelated to venous thromboembolism risk. Moreover, the switching argument was an unlikely explanation for the findings of the key studies because women with a past history of venous thromboembolism were

excluded (Walker 1998). A reanalysis of data from the Leiden Thrombophilia Study confirmed that the risk of venous thromboembolism was highest in first-time users of oral contraceptives, but this effect was only partly explained by the presence of clotting defects such as the factor V Leiden mutation, protein C or S deficiency, antithrombin deficiency, and prothrombin G20210A mutation and it did not explain the difference in risk between oral contraceptives containing different progestogens (Bloemenkamp et al. 2000).

Referral and diagnostic biases

Some commentators suggested that women taking contraceptives containing desogestrel or gestodene were more likely to be referred for investigation of symptoms suggestive of venous thromboembolism than users of other preparations — thus, true cases with ambiguous symptoms would be counted if they were taking desogestrel or gestodene pills but not if they were taking older preparations (Rosenberg et al. 1996; Cohen 1996a; Lidegaard and Milsom 1996a; Lewis et al. 1996b; Spitzer 1997). The Transnational investigators also made a rather extraordinary statement about the conduct of their own study:

> Bias could have arisen in the study if recruiting physicians, with the best of intentions, actively recruited women using the pill who developed the disease of interest. We believe that this might have happened in some instances, which would artificially inflate the risk" (Davis et al. 1995).

Such bias, however, would not explain a differential risk between users of different contraceptive preparations. For referral bias to be a credible explanation for the observed excess risk of venous thromboembolism in users of desogestrel and gestodene contraceptives compared with older formulations, two conditions should have been met. First, doctors would have needed to believe that users of these pills had a higher risk of venous thromboembolism than users of older formulations (Walker 1999). Moreover, they would have needed to act on that belief by preferentially referring such users for diagnostic assessment. Second, the perception of risk would have needed to be independent of any known pre-existing risk factors for venous thromboembolism since, as discussed above, such factors were accounted for in the analyses (Walker 1998).

In fact, there were several reasons to reject referral bias as an explanation for the excess risk. First, the argument that users of desogestrel and gestodene contraceptives had

been preferentially referred ran counter to the marketing messages that these pills were safer (Walker 1998). Second, reviews of doctors' attitudes and clinical practices gave no indication that such referral practices had occurred (Heinemann et al. 1996; Dunn et al. 1998). Third, even if such a bias was functioning, the excess risk should only have been apparent among women whose symptoms and signs of venous thromboembolism were less definite (Vandenbroucke et al. 1997a). However, analyses in which cases were stratified by certainty of diagnosis were undertaken in three of the studies, including the Transnational study, and these showed an elevated risk for both definite and less probable cases (Jick et al. 1995; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995b; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995c; Spitzer et al. 1996). Fourth, the risk estimates obtained from a study based on the MediPlus database in the UK, which included non-hospitalised as well as hospitalised cases (Farmer 1996), were similar to those obtained in the key studies (Farley et al. 1996). Finally, the results of two later case-control studies suggested that it was unlikely that referral and diagnostic biases were operating (Realini et al. 1997; Bloemenkamp et al. 1999). In both of these studies, the study population consisted of women who were referred for investigation of suspected venous thromboembolism — those who were found to have objective evidence of thrombosis became cases and those who did not became controls. Among women without major risk factors for venous thromboembolism, the adjusted relative risk estimates obtained for oral contraceptive use were very similar in magnitude to those found for any pill use in the key studies.

In relation to possible diagnostic bias, several commentators were concerned about the difficulties in reliably diagnosing venous thromboembolism (Johannisson and The International Committee for Research in Reproduction 1996). However it was argued that if any misclassification of diagnosis had occurred, then the effect would have been to underestimate the true relative risk (Jick et al. 1996a; Vandenbroucke et al. 1996a). In fact, the results of analyses stratified by certainty of diagnosis implied that such misclassification had not played a role in the WHO study (Poulter et al. 1996a).

Residual confounding

Although, as shown earlier, confounding by indication failed to explain the higher risk of venous thromboembolism observed in users of desogestrel and gestodene oral contraceptives, one group argued that the risk estimates in the key studies were distorted by residual confounding by age (Farmer et al. 1997a). These researchers undertook a cohort analysis based on the MediPlus database in the UK in which they adjusted for age in five-year bands; the relative risk of venous thromboembolism in users of desogestrel and gestodene pills compared with users of levonorgestrel and other "second generation" (undefined) products was 1.68 (95% CI 1.04 – 2.75). Next, a nested case-control analysis was conducted in which controls were matched with cases by exact year of birth; the odds ratio in this analysis was only 1.34 (95% CI 0.74 – 2.39). However, following the publication of the preliminary (Farmer 1996) and detailed (Farmer et al. 1997a) findings of this study the researchers were criticised for including non-hospitalised and unverified cases (Jick et al. 1996a; Poulter et al. 1996a; Jick et al. 1997; Poulter et al. 1997; Vandenbroucke et al. 1997b) and for entering inappropriate variables into the logistic regression model (Poulter et al. 1997; Vandenbroucke et al. 1997b). Moreover, it was argued that finer age matching was an implausible explanation for the reported decrease in relative risk because adjustment for age in the cohort analysis had actually moved the estimate further away from the null value (Walker 1998).

The authors of three of the key studies maintained that their results could not be explained by residual confounding by age — the odds ratios in the Leiden study had been adjusted by single year of age (Vandenbroucke et al. 1997b) and the excess risk for desogestrel and gestodene pills persisted in both the WHO (Poulter et al. 1997) and the GPRD (Jick et al. 1997) studies when the data were reanalysed using finer age matching. Similarly, adjusting for age in one-year, compared with five-year, age groups had little impact on the results of the Danish case-control study discussed earlier (Lidegaard et al. 1998).

Nonetheless, the MediPlus investigators continued in their quest to demonstrate that the excess risk of venous thromboembolism in users of desogestrel and gestodene preparations was not real. First, they undertook another case-control study based on the

German MediPlus database; the unadjusted odds ratio for users of third generation (undefined) compared with users of second generation (undefined) pills was not elevated (Farmer et al. 1998a; Farmer et al. 1998b). It was not possible to explore potential confounding by BMI and other risk factors because of missing data. Second, the UK MediPlus study was reanalysed using a further 18 months' worth of data and an attempt was made to validate the diagnosis of venous thromboembolism in a sample of cases (Todd et al. 1999). However, this analysis was criticised because the investigators adjusted for the number of prescriptions issued for medications other than oral contraceptives in the six months before the index date, thereby potentially adjusting for early manifestations of venous thromboembolism (Farley et al. 1999). Third, the investigators performed a nested case-control study, based on venous thromboembolic events recorded in the UK GPRD between 1992 and 1997 (Farmer et al. 1999; Farmer et al. 2000a). Matching controls to cases by year of birth, compared with five-year age bands, inconsistently produced slightly lower estimates of relative risk. The researchers, who had earlier criticised the practice of aggregating oral contraceptives by progestogen component (Todd et al. 1999), estimated relative risks for individual oral contraceptives; products containing desogestrel and gestodene were not shown to carry a higher risk than other preparations.

3.2.7 Consideration of trends in oral contraceptive use and venous thromboembolism

Soon after the publication of the key studies, it was claimed that the uptake of desogestrel and gestodene pills had not been accompanied by an increase in the incidence of venous thromboembolism among women of child-bearing age — an increase which should have been apparent, it was argued, if such oral contraceptives truly carried an excess risk (Lidegaard and Milsom 1996a). However, mortality trends among young women in England and Wales (Thomas 1996a) and the Netherlands (Vandenbroucke et al. 1996b) appeared to be consistent with an increased risk, and alternative interpretations (Farmer and Lewis 1996; van Lunsen 1996b; Cohen 1996b) failed to explain these trends (Thomas 1996b; Vandenbroucke et al. 1996c). Subsequently an attempt was made to compare mortality among users of different oral contraceptive preparations and non-users using sales and mortality data from seven European countries (Farmer et al. 1997b). However, it was not possible to standardise for age and, in any case, the study lacked sufficient power to detect any differences. Later, Danish investigators reported a 16% increase in admissions for venous

thromboembolism in women aged 15 – 49 years concurrent with increased use of desogestrel, gestodene, and norgestimate in Denmark (Mellemkjaer et al. 1999). Increased admissions were also described in the Oxford region during the same period, however these were not confined to women or to women of child-bearing age (Goldacre et al. 2000).

3.2.8 Consideration of biological plausibility

An argument that was initially used to reject the findings of an excess risk of venous thromboembolism in users of desogestrel and gestodene contraceptives was that there was no biologically plausible explanation for such an effect (Johannisson and The International Committee for Research in Reproduction 1996; Westhoff 1996; Lidegaard and Milsom 1996a; Spitzer 1997; Winkler 1998; Speroff 1999a). One commentator went so far as to challenge the role of epidemiologists in researching venous thromboembolism and oral contraceptives, asserting that:

> It is the clinical endocrinologist, not the epidemiologist, who has the depth and breadth of knowledge of steroid biochemistry, molecular and cellular endocrinology, and endocrine physiology to scientifically design the critical experiments in this arena (Barbieri 1999).

However, it was promptly argued that the lack of a biological explanation was not grounds to reject the observed association (Farley et al. 1996). Indeed, as one commentator eloquently observed:

> The lack of in vitro support for a theory that is based in real-world observation is seldom a crucial flaw. In drug research, it is almost tautological that serious adverse effects will not have a well understood physiologic basis when they are first observed. If the warning from preclinical studies had been in place, the drug would not likely have been marketed (Walker 1998).

Moreover, a possible mechanism was subsequently reported. Compared with non-users, women taking oral contraceptives were shown to have a reduction in normal anticoagulant activity secondary to enhanced resistance to activated protein C, similar to that observed in carriers of the factor V Leiden mutation. This effect was more pronounced in women taking contraceptives containing desogestrel or gestodene than users of levonorgestrel or lynoestrenol preparations (Rosing et al. 1997). These findings were confirmed in a randomised cross-over trial of desogestrel and levonorgestrel oral contraceptives (Rosing et al. 1999).

3.2.9 Consideration of the magnitude of any difference in risk

Some commentators asserted from early on that even if desogestrel and gestodene oral contraceptives really did carry a higher risk of venous thromboembolism than older products, the magnitude of the difference in risk in both relative and absolute terms was very small (Spitzer 1995; Guillebaud 1995a; Rosenberg et al. 1996). The principal investigator of the Transnational study later stated that "relative risks of about 2 even if real, are clinically unimportant and of no public health significance" (Spitzer 1997).

However, there were several reasons to challenge this position. First, a small increase in risk has the potential to affect a large number of women simply because of the extensive use of oral contraceptives (World Health Organization 1997). Second, the majority of venous thromboembolic events in young women are attributable to oral contraceptive use (Rosendaal 1999b). Third, although the case-fatality rate is thought to be low, venous thromboembolism nonetheless can have substantial short and long-term consequences for those affected (Skegg 1997). Finally, reports that venous thromboembolism is rare among oral contraceptive users are unlikely to be of comfort to any woman who suffers a potentially avoidable event while taking a desogestrel or gestodene contraceptive, especially if an alternative with half the risk is available.

3.2.10 Consideration of other benefits of desogestrel and gestodene oral contraceptives

Immediately after the CSM warning, several commentators suggested that oral contraceptives containing desogestrel and gestodene might confer other benefits that would outweigh any excess risk of venous thromboembolism. While the contraceptive efficacy of the newer contraceptives appeared to be equivalent to older preparations (Speroff et al. 1993), it was suggested that they were associated with fewer so-called minor side-effects (Guillebaud 1995a) and possibly lower risks of myocardial infarction (Spitzer 1995) and stroke (Guillebaud 1995a). Moreover, it was argued that although the latter two conditions were rare in young women, they carried a higher case-fatality rate than venous thromboembolic events (MacRae and Kay 1995). Thus, it was proposed that desogestrel and gestodene contraceptives could be preferentially prescribed to women with risk factors for arterial thrombosis (Guillebaud 1995a).

Minor side-effects

In response to anecdotal reports that desogestrel and gestodene contraceptives were better tolerated by women (Guillebaud 1995a), several commentators (O'Brien 1995; Paul 1996), including the principal investigator of the Transnational study (Spitzer 1996), soon pointed out that there was very little evidence from well-designed studies to support such claims. Indeed, one pharmaceutical company was subsequently ordered by the Food and Drug Administration in the USA to withdraw advertising material which maintained that oral contraceptives containing desogestrel caused fewer minor side-effects than other preparations because there was no "adequate substantiation from well-controlled clinical trials" to support such statements (Stockbridge 1998).

Myocardial infarction

As discussed earlier, because they had fewer adverse effects on blood coagulation and lipoprotein and carbohydrate metabolism, there was an expectation that desogestrel and gestodene oral contraceptives would carry a lower risk of myocardial infarction than older products. However, it was not until immediately after the CSM warning that the first epidemiological data were made available (Spitzer 1995). Interim results from the Transnational case-control study of myocardial infarction were consistent with a lower risk in users of desogestrel and gestodene contraceptives, although this effect was not statistically significant (Lewis et al. 1996c). In later analyses, it appeared that users of these oral contraceptives did not have an increased risk of myocardial infarction when compared with non-users, whereas a significant increase was found for users of older preparations (Lewis et al. 1997). However this picture was not consistent. For instance, a significantly lower risk for desogestrel and gestodene products, compared with levonorgestrel, was observed in Europe, but not in the UK, and was found in women aged 35 – 44 years (in whom oral contraceptive use was uncommon), but not in younger women.

Other studies based on events which occurred before the CSM warning did not support the contention that, compared with non-users, women taking older oral contraceptives had an increased risk of myocardial infarction whereas users of desogestrel or gestodene preparations did not. In the WHO case-control study of myocardial infarction, an increased risk in oral contraceptive users was confined to those women whose blood pressure was not checked and those with cardiovascular risk factors (World Health

Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1997). Limited power precluded an analysis by type of progestogen. Similarly, in a case-control study based on the Kaiser Permanente Health Care Database, use of low-dose oral contraceptives was not associated with a significantly increased risk of myocardial infarction (Sidney et al. 1996). Moreover, a nested case-control study undertaken by researchers at the Boston Collaborative Drug Surveillance Program, which was based on the UK GPRD, revealed no significant difference in myocardial infarction risk between current users of desogestrel and gestodene products compared with levonorgestrel preparations (Jick et al. 1996b), while a community-based case-control study in England, Scotland, and Wales showed a non-significant elevated point estimate for desogestrel and gestodene contraceptives compared with levonorgestrel and norethisterone preparations (Dunn et al. 1999). Finally, it was reported that trends in fatal myocardial infarction in young women in England and Wales (Thomas 1996a) and the Netherlands (Vandenbroucke et al. 1996b) were not consistent with a protective effect of desogestrel and gestodene.

Stroke

In two of the case-control studies of ischaemic stroke published following the CSM warning, current users of oral contraceptives did not have a higher risk than non-users (Petitti et al. 1996; Schwartz et al. 1997) whereas in three other studies, current users carried a higher risk (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1996a; Heinemann et al. 1997; Lidegaard and Kreiner 1998). One group reported that the elevated risk was confined to women who were using oral contraceptives other than those containing desogestrel or gestodene (Lidegaard and Kreiner 1998). In the WHO study, when compared with non-use, levonorgestrel pills appeared to carry a higher risk than desogestrel or gestodene preparations, but the difference disappeared when blood pressure checks were taken into account (Poulter et al. 1999b). In the Transnational study no significant difference in risk by progestogen component was found among women who had their blood pressure monitored (Heinemann et al. 1997).

As with ischaemic stroke, no increased risk of haemorrhagic stroke was found overall for users of oral contraceptives in the two case-control studies from the USA (Petitti et al. 1996; Schwartz et al. 1997). In the latter study, however, an increased risk was

found for contraceptives containing norgestrel-type progestogens (levonorgestrel or norgestrel), but not norethindrone-type progestogens (norethindrone, norethindrone acetate, ethynodiol diacetate, or norethynodrel); no comment was made about other types of progestogens. In the WHO study, an increased risk of haemorrhagic stroke was found only in older women who were taking contraceptives (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1996b). The risk did not vary by progestogen constituent (Poulter et al. 1999b). A study undertaken by the Boston group, which was based on the UK GPRD, found no difference in risk of cerebral haemorrhage among oral contraceptive users according to progestogen type (Jick et al. 1999).

Thus, in summary, there was no convincing evidence that desogestrel and gestodene contraceptives conferred particular benefits over older preparations. Moreover, arguments about whether certain oral contraceptives carried a lower risk of myocardial infarction or stroke were irrelevant for the majority of pill users — that is, women less than 30 years of age in whom such outcomes are extremely rare (Paul 1996). In fact, using relative risk estimates from the WHO study and incidence rates from the Oxford region, the WHO investigators demonstrated that the potentially avoidable excess of venous thromboembolic events in women who used desogestrel or gestodene contraceptives would represent a considerable proportion of the total cardiovascular morbidity in women aged less than 35 years (Farley et al. 1998b).

3.2.11 Consideration of comparisons of risk

A comment that was frequently heard during the debate about the safety of oral contraceptives containing desogestrel and gestodene was that the absolute risk of venous thromboembolism in users of these pills was much lower than that encountered during pregnancy (Farmer and Preston 1995; Guillebaud 1995a; Leader 1996; Westhoff 1996). The implication was, therefore, that the ongoing use of such contraceptives was justified. However, such a line of reasoning would only be coherent if desogestrel and gestodene contraceptives were the sole means by which pregnancy could be prevented.

In any case, a nested case-control study confined to women aged < 50 years in the UK GPRD who had been prescribed the emergency contraceptive pill at any time during an eight-year period suggested that the absolute risk difference might not be as large as was

believed; the crude rates of idiopathic venous thromboembolism per 100,000 women-years at risk were 15.5 (6.6 – 36.3) for pregnancy and the puerperium, 10.7 (4.9 – 23.3) for users of desogestrel or gestodene pills, and 5.3 (95% CI 1.4 – 19.2) for users of low-dose levonorgestrel oral contraceptives (Vasilakis et al. 1999b).

3.2.12 Consideration of competing interests

By the end of 1998, three independently funded analytical studies had been published which showed a two-fold excess risk of venous thromboembolism in users of oral contraceptives containing desogestrel or gestodene, when compared with users of older preparations (Bloemenkamp et al. 1995; Jick et al. 1995; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995c). Conversely, three studies directly funded by the pharmaceutical industry had shown relative risks of 1.5 or less (Spitzer et al. 1996; Farmer et al. 1997a; Lidegaard et al. 1998). These findings prompted questions about the influence of competing interests (Vandenbroucke 1998).

While the authors of the three key studies which were independently funded remained convinced that the apparent excess risk of venous thromboembolism observed in users of desogestrel and gestodene oral contraceptives was real (Helmerhorst et al. 1997; Jick et al. 1997; Vandenbroucke et al. 1997a; Vandenbroucke 1998; Farley et al. 1998c; Farley et al. 1999), the Transnational researchers continued to argue that the association was explained by bias and confounding (Spitzer 1997; Lewis 1998; Spitzer 1998a; Spitzer 1998b; Heinemann 1999; Spitzer 1999) and subjected their study to four reanalyses.

The second group of investigators who undertook industry-funded research recycled accounts of their UK MediPlus study research (Farmer 1996; Farmer et al. 1997a; Farmer and Lawrenson 1998; Farmer et al. 1999) and later subjected the data to a reanalysis (Todd et al. 1999). The same researchers also published the results of their studies based on the German MediPlus (Farmer and Lawrenson 1998; Farmer et al. 1998a; Farmer et al. 1998b; Farmer et al. 1999) and UK GPRD (Farmer et al. 1999; Farmer et al. 2000a) databases more than once.

As well as funding reanalyses and new studies, one commentator observed that "three multinational companies have used enormous marketing resources to sow confusion", subjecting individual doctors and various organisations to an "avalanche of special symposia and paid supplements" (Vandenbroucke et al. 2000). Indeed, a striking relationship can be observed between funding sources and the conclusions drawn by commentators about the likely explanations for the observed excess risk of venous thromboembolism in users of desogestrel and gestodene contraceptives. For instance, consensus statements and reviews by researchers who were not involved in the key studies, and who were known to have received funding from pharmaceutical companies at some point, tended to attribute at least part, if not all, of the excess risk to bias and confounding (Lidegaard and Milsom 1996; Rosenberg et al. 1996; Cohen 1996a; Lidegaard and Milsom 1996a; Carr and Ory 1997; Rosenberg et al. 1997; Chasan-Taber and Stampfer 1998; Ory 1998; Cohen 1999; Lidegaard et al. 1999; Speroff 1999a; Speroff 1999b). Conversely, reviews by several independent commentators who were not involved in the key studies (Paul 1996; Skegg 1997; Walker 1998; LeBlanc and Laws 1999; Maling 1999; McPherson 1999; O'Brien 1999; Walker 1999; Weiss 1999; Hannaford 2000), as well as a scientific group convened by WHO (World Health Organization 1997; World Health Organization 1998), all concluded that the excess risk could not be explained by bias or confounding.

3.2.13 Summary

By the end of the 1990s, the relationship between modern low-dose oral contraceptives and venous thromboembolism had been clarified and largely accepted. First, compared with non-users, current users of any oral contraceptive had a three to six-fold increased risk of venous thromboembolism (World Health Organization 1998). Second, this risk appeared to be greatest in the first year of use, although an elevated risk persisted until oral contraceptives were discontinued (World Health Organization 1998). Third, the risk declined to the same level as non-users within three months of discontinuation (World Health Organization 1998). Fourth, the risk in users of pills containing < 50μg ethinyloestradiol seemed to be unrelated to oestrogen dose (World Health Organization 1998). Fifth, the proposed non-causal explanations for the difference in risk between desogestrel and gestodene contraceptives and other preparations had failed to account for the observed results (World Health Organization 1998). Moreover, there was sufficient evidence to confirm a causal relationship between the use of desogestrel and

gestodene contraceptives and an excess risk of venous thromboembolism. Compared with current users of levonorgestrel and norgestrel oral contraceptives, users of desogestrel and gestodene pills had about twice the risk of venous thromboembolism (summary odds ratio 1.9 [95% CI 1.5 – 2.2]) (Farley et al. 1999). Sixth, oral contraceptive users who were carriers of hereditary clotting defects such as factor V Leiden, protein C or S deficiency, and antithrombin deficiency had been shown to have much higher risks of venous thromboembolism than users without such abnormalities (World Health Organization 1998). Conversely, the relationship between oral contraceptives and venous thromboembolism was not modified by age, smoking, or the presence of varicose veins (World Health Organization 1998). The data about BMI were inconsistent (World Health Organization 1998). Seventh, the incidence of idiopathic venous thromboembolism (per 10,000 women per year) in young women was estimated to be about 0.5 – 1 in non-users, three to four times this baseline rate in users of levonorgestrel preparations, and six to eight times higher in users of desogestrel and gestodene contraceptives (Vandenbroucke et al. 1997a). Eighth, a biologically plausible explanation for the excess risk of venous thromboembolism in users of desogestrel and gestodene contraceptives had been identified with the discovery that women using these contraceptives had a greater resistance to activated protein C than users of levonorgestrel pills (Farley et al. 1999). Finally, suggestions that the higher risk of venous thromboembolism would be outweighed by other benefits of desogestrel and gestodene contraceptives, such as a lower incidence of myocardial infarction and stroke, had not been borne out (Farley et al. 1999).

3.3 PSYCHOTROPIC DRUGS AND VENOUS THROMBOEMBOLISM

3.3.1 Case reports and case series

Shortly after the introduction of the first antipsychotic medications in the early 1950s, several reports of venous thromboembolic events among users of these drugs were published (Brehmer and Ruckdeschel 1953; Labhardt 1954; Maurice 1956; Mielke 1956; Grahmann and Suchenwirth 1959). Interestingly, these and the sporadic case reports and case series which emerged over the next few decades (Mahmodian 1963; Häfner and Brehm 1965; Meier-Ewert et al. 1967; Scholz 1967; Lunel et al. 1972; Singer et al. 1975; Ruh-Bernhardt et al. 1976), were confined to patients in continental

Europe. Such reports suggested that venous thromboembolism was an important cause of morbidity in patients receiving psychotropic drugs; in one series of 1,590 patients treated with neuroleptic medication, it was the most common fatal adverse drug reaction (Häfner and Brehm 1965). In this study and two others, the incidence of venous thromboembolism in psychiatric patients who received antipsychotic drugs (Grahmann and Suchenwirth 1959), and those who were given either antipsychotics or tricyclic antidepressants (Häfner and Brehm 1965; Meier-Ewert et al. 1967), was compared with patients who received either very low doses of these drugs or other treatments. Venous thromboembolic events were significantly more common in the groups treated with antipsychotic and antidepressant drugs. It was thought that immobilisation, rather than any direct effect of the drugs on the coagulation system, was responsible. It should be noted, however, that these analyses were very crude and the underlying characteristics of the patients in the treatment and comparison groups are likely to have differed.

More recently, reports of venous thromboembolism in users of conventional (Varia et al. 1983; Roche-Bayard et al. 1990; McCall et al. 1995; Kamijo et al. 2003) and atypical antipsychotics such as clozapine (Clardy and Gale 1995; Lacika and Cooper 1999; Coodin and Ballegeer 2000; Hägg et al. 2000; Knudson et al. 2000; Maynes 2000; Modai et al. 2000; Suttmann et al. 2000; Ihde-Scholl et al. 2001; Farah et al. 2004), risperidone (Kamijo et al. 2003), and zotepine (Pantel et al. 1997) have appeared in the English language literature. In the absence of a comparison group, however, such reports are only ever suggestive of a relationship. Indeed, results from a surveillance programme of severe adverse drug reactions in Swiss and German psychiatric inpatients are consistent with no association; the crude rates of venous thromboembolism were similar in those treated with clozapine, those given other neuroleptics, and those who received no such medicines (Wolstein et al. 2000).

Several reports have described the occurrence of venous thromboembolism in patients taking various antidepressant regimens, including tricyclic antidepressants taken with or without antipsychotics (Häfner and Brehm 1965; Meier-Ewert et al. 1967; Singer et al. 1975; Ruh-Bernhardt et al. 1976; Hägg et al. 2000), selective serotonin-reuptake inhibitors (SSRIs) used in conjunction with antipsychotics (Pantel et al. 1997; Maynes 2000; Farah et al. 2004), SSRI use during a period of immobilisation (Arnone et al.

2002), and the use of unspecified antidepressants and antipsychotics with lithium carbonate (Kallner et al. 2000).

Other reports, while making no reference to medication, have described the occurrence of venous thromboembolism among psychiatric patients in general (Lal et al. 1966; Kendel and Fodor 1969; Ziegler 1977; Hindersin et al. 1984; Hewer et al. 1995), and more particularly with catatonic or depressive stupor (Sukov 1972; O'Brien 1991; McCall et al. 1995; Morioka et al. 1997; Arnone et al. 2002) and physical restraint (Hem et al. 2001; Lazarus 2001; Ramirez et al. 2001).

3.3.2 Analytical studies

Four decades after the first case reports, the potential association between psychotropic drugs and venous thromboembolism was finally explored in well-designed analytical studies. The first study to find an association was a case-control study of cardiovascular mortality in English and Welsh women of child-bearing age (Thorogood et al. 1992a). An incidental finding in this study, which was designed to examine the risks of fatal cardiovascular events associated with oral contraceptive use, was a 17-fold increased risk of myocardial infarction among users of psychotropic drugs, particularly tricyclic antidepressants and benzodiazepines. In addition, an almost three-fold increased risk of pulmonary embolism in current users of psychotropics was found, although no point estimates were reported for individual drug groups.

Subsequently several studies were undertaken with the primary aim of examining the risk of venous thromboembolism in users of psychotropic drugs, in general, or antipsychotic medicines in particular. These studies are outlined in Tables 3.4 and 3.5.

Table 3.4 Case-control studies of psychotropic drug use and venous thromboembolism

Reference	Study design	Cases	Controls	Exposure information	Adjustment factors	Results
(Zornberg and Jick 2000)	Nested case-control study of idiopathic VTE based on UK GPRD. Study population: patients aged < 60 years who received ≥ 1 prescriptions for conventional or atypical antipsychotic drugs between January 1990 and October 1998. Excluded all patients with previous DVT, PE, or MI; those with coagulopathies congestive heart failure, cancer, renal failure, epilepsy, diabetes, cystic fibrosis, multiple sclerosis, alcohol or substance abuse; pregnancy, trauma or surgery < 6 months before index date; an acute psychotic episode < 2 months before index date. Also those with < 6 months recorded clinical data before first prescription for an antipsychotic.	Ascertainment Reviewed electronic GP records to identify women who were admitted to hospital with objectively diagnosed DVT and / or PE and anticoagulated. Examined hospital discharge letters and death certificates to verify diagnosis. Index date Date of diagnosis. Total included n = 42 (2 fatal)	Selection For each case, randomly selected 4 controls from study population. Matching factors GP, sex, age (year of birth), years in GPRD. Index date Index date of case. Total included n = 168	Details of psychotropic (antipsychotic, antidepressant) exposure and other data abstracted from electronic records. Most psychotropic drug prescriptions for 1 months' supply. Current use of psychotropic drugs Prescribed use ≤ 30 days before index date. Recent use of psychotropic drugs Prescribed use 31 – 90 days before index date. Non-use of psychotropic drugs No prescribed use ≤ 90 days before index date. Reference categories 1. Non-users. 2. Non-users and recent users. Current use of oestrogens Receipt of prescription for oral / transdermal / parenteral contraception or HRT < 180 days before index date. Recent use of oestrogens Receipt of prescription 180 – 365 days before index date.	Smoking, BMI, hypertension, oestrogen use, and antidepressant use.	**Adjusted matched OR (95% CI) for use of antipsychotic** ***Non-users as reference*** Current use any antipsychotic: 7.1 (2.3 – 21.97) Recent use any antipsychotic: 2.1 (0.4 – 11.8) ***Non-users and recent users as reference*** Current use low potency antipsychotic: 24.1 (3.3 – 172.7) Current use high potency antipsychotic: 3.3 (0.8 – 13.2) Current use any antipsychotic: < 12 months: 28.7 (4.9 – 169.5) Current use any antipsychotic: ≥ 12 months: 1.0 (0.1 – 7.3) **Unadjusted unmatched OR (95% CI) for use of antidepressant** ***Non-users as reference*** Current use any antidepressant: 1.7 (0.8 – 3.7)

Reference	Study design	Cases	Controls	Exposure information	Adjustment factors	Results
(Thomassen et al. 2001)	Reanalysis of Leiden Thrombophilia Study, a population-based case-control study of consecutive men and women aged < 70 years with a 1st diagnosis of DVT between January 1988 and December 1992. Patients with known malignancy excluded.	Ascertainment Examined files of anticoagulation clinics in 3 regions in the Netherlands to identify cases with objectively diagnosed DVT. Index date Date of DVT. Total included n = 474	Selection Each case was asked to find a friend or acquaintance of the same sex and age, who was not a biological relative, had no history of VTE or malignancy, and did not use warfarin, to serve as a control. Cases who were unable to find a suitable control were matched with partners of other cases. Matching factors Sex and age. Index date Index date of case. Total included n = 474	Cases and controls both interviewed 6 – 19 months after index date (1990 – 1993) about risk factors for DVT, including medication use and a history of VTE in ≥ 1 parent or sibling. Physical examination undertaken and blood collected for coagulation factor and FVL analysis. Use of psychotropic drugs Defined as daily use. Reference category Non-users.	Nil	4 cases and no controls used antipsychotic drugs in year before index date. **Unadjusted unmatched OR (95% CI)** ***Non-users as reference*** Use of antidepressant in year before index date: 2.3 (0.6 – 10.2). **Unadjusted unmatched OR (95% CI)** ***Non-users as reference*** Use of benzodiazepine in year before index date: 4.2 (1.8 – 11.5).

Abbreviations used in the table BMI: body mass index, DVT: deep vein thrombosis, GP: general practice, HRT: hormone replacement therapy, MI: myocardial infarction, OR: odds ratio, PE: pulmonary embolism, VTE: venous thromboembolism.

Table 3.5 Cohort studies of psychotropic drug use and venous thromboembolism

Reference	Participants	Exposure and outcome information	Incidence per 100,000 person-years (number of events)	Results
(Walker et al. 1997)	Study population 67,072 patients aged 10 – 94 years who were enrolled on the national registry of clozapine users (Clozaril National Registry) in the USA and had a record of receiving at least 1 weeks' supply of clozapine at any time between April 1991 and December 1993. Excluded patients with post codes from New York City, as death certificates not available for these patients. Key analyses confined to patients aged 10 – 54 years. Current users of clozapine ≤ 14 days since last record in Registry of active use. Recent users of clozapine 15 to 106 days since last record in Registry of active use. Comparison group (former users) ≥ 107 days since last record in Registry of active use.	Linked data from Clozaril National Registry with National Death Index and Social Security Administration Death Master files using patients' Social Security Numbers. Deaths certificates examined by professional nosologist, coded underlying cause of death according to ICD-9. The Registry contained details of mandatory WBC counts (a pre-treatment test, weekly tests during therapy, and weekly tests for 4 weeks following discontinuation of medicine) for all clozapine users, as well as dosage information (clozapine supplies were dispensed weekly). Each WBC record indicated whether clozapine being actively received by patient, on-hold (temporarily stopped), or discontinued.	**Adjusted mortality rates** All causes Past users: 693 (111) Recent users: 1,174 (89) Current users: 322 (196) PE Past users: 6 (1) Recent users: 0 Current users: 30 (18) Conduction disorders or sudden death Past users: 7 (1) Recent users: 28 (2) Current users: 15 (9) Respiratory diseases Past users: 11 (2) Recent users: 114 (9) Current users: 33 (20) Suicide Past users: 222 (33) Recent users: 246 (18) Current users: 39 (24) Rates adjusted for sex, age, and ethnicity.	**Adjusted RR (95% CI) for use of clozapine** ***Past users as reference*** All causes Recent use: 1.69 (1.28 – 2.25) Current use: 0.46 (0.37 – 0.59) PE Recent use: 0.0 Current use: 5.2, 95% CI not computed. Conduction disorders or sudden death Recent use: 4.19, 95% CI not computed Current use: 2.22, 95% CI not computed. Respiratory diseases Recent use: 9.96, 95% CI not computed Current use: 2.92, 95% CI not computed. Suicide Recent use: 1.11 (0.62 – 1.99) Current use: 0.17 (0.10 – 0.30) **Other results** Standardised mortality ratio (95% CI) for cohort (current, recent, past users combined) compared with general population: 1.73 (1.56 – 1.91).

Reference	Participants	Exposure and outcome information	Incidence per 100,000 person-years (number of events)	Results
(Ray et al. 2002)	131,196 patients aged ≥ 65 years who were enrolled with the Ontario Health Insurance Plan and were prescribed antipsychotic drugs (n = 22,514), antidepressants (n = 75,649), or thyroid replacement hormones (n = 33,033) between January 1994 and March 2000. Excluded patients who had taken any of the study drugs in the year before January 1994; those who had not filled ≥ 2 prescriptions for study drug within 180 days of its initiation; those who concurrently (within 1 year) took drugs from > 1 category; users of warfarin < 1 year before study entry; and patients diagnosed with cancer or VTE < 3 years before study entry. Users of antipsychotics ≤ 180 days since last prescription. Users of antidepressants ≤ 180 days since last prescription. Comparison group Users of thyroid replacement therapy, ≤ 180 days since last prescription.	To identify VTE events, new cancer diagnoses, and other hospitalisations, used patients' unique healthcare numbers to link prescription data with hospital discharge and outpatient databases.	**Crude incidence** DVT only Antipsychotic users: 1650 (307) Antidepressant users: 1160 (812) Thyroid replacement therapy users: 1010 (593) DVT and / or PE Antipsychotic users: 1920 (357) Antidepressant users: 1430 (999) Thyroid replacement therapy users: 1200 (703) Number of events derived from data in paper.	**Adjusted hazard ratio (95% CI) for current use of psychotropic drug** ***Thyroid replacement users as reference*** DVT only Any antipsychotic: 1.13 (0.97 – 1.32) Phenothiazine: 0.86 (0.67 – 1.10) Dibenzothiazepine: 1.13 (0.83 – 1.55) Butyrophenone: 1.51 (1.23 – 1.86) Any antidepressant: 1.02 (0.91 – 1.13) SSRI: 1.00 (0.88 – 1.14) Tricyclic: 0.98 (0.85 – 1.13) Benzisoxazole: 0.73 (0.34 – 1.54) DVT and / or PE Any antipsychotic: 1.10 (0.95 – 1.27) Phenothiazine: 0.83 (0.66 – 1.05) Dibenzothiazepine: 1.19 (0.90 – 1.58) Butyrophenone: 1.43 (1.18 – 1.74) Any antidepressant: 1.04 (0.94 – 1.15) SSRI: 1.04 (0.92 – 1.17) Tricyclic: 0.98 (0.86 – 1.11) Benzisoxazole: 0.70 (0.35 – 1.41) Hazard ratios adjusted for sex, age, currently residing in a long-term care facility, recent hospitalisation, concurrent diagnosis of cancer, and concurrent prescription of aspirin, warfarin, oestrogen, or lithium.

Abbreviations used in the table DVT: deep vein thrombosis, ICD: International Classification of Diseases, PE: pulmonary embolism, RR: relative risk, VTE: venous thromboembolism, WBC: white blood cell.

As can be seen from the tables above, the first analytical study which was specifically designed to examine the risk of venous thromboembolism in users of antipsychotics was confined to an atypical preparation (Walker et al. 1997). In this cohort study, data from a national registry of clozapine users in the USA were linked with death registrations in order to explore the overall and cause-specific mortality in current and past users. Among patients aged 10 – 54 years, the sex, age, and ethnicity-adjusted mortality rate for pulmonary embolism in current users was five times that of past users. The risk of conduction disorders or sudden death was also elevated in current and recent users. Because necropsies were undertaken in only 54% of deaths (63% in current users), it is possible that the underlying causes of some deaths were misclassified. If, for example, some pulmonary embolism deaths in current users were misclassified as conduction disorders or sudden death, then the risk of fatal venous thromboembolism in current users of clozapine might have been underestimated. A second feature of the study which might have led to an attenuation of the relative risk was the use of past users of clozapine as the reference category. The major advantage of using this internal comparison group was that it provided some control for confounding by factors such as the severity of schizophrenia and the prescribing preferences of physicians. However, because the use of clozapine during the study period was restricted to patients with severe schizophrenia, it is unlikely that every past user of clozapine had discontinued antipsychotic use altogether. Thus, if other antipsychotics also carried an increased risk of venous thromboembolism, then the risk associated with current use of clozapine could have been underestimated.

A nested case-control study, undertaken by researchers at the Boston Collaborative Drug Surveillance Program and based on the UK GPRD, explored the association between the outpatient use of conventional antipsychotic medication and first-time idiopathic venous thromboembolism (Zornberg and Jick 2000). Only two cases (one current and one past user) were fatal. Current use ($\leq$ 30 days before the index date) was associated with a seven-fold increase in risk when compared with non-use (adjusted odds ratio 7.1 [95% CI 2.3 – 21.9]). The risk appeared to be highest during the first few months of use which led the investigators to suggest that some people might be predisposed to antipsychotic-induced venous thromboembolism. The odds ratios for current use of antipsychotics did not differ by the chemical class, nor were higher doses of particular drugs associated with higher risks of venous thromboembolism. However,

the relative risk estimates did vary by potency, that is, the dose required to achieve a therapeutic effect. Low potency antipsychotics such as chlorpromazine and thioridazine carried a higher risk than high potency drugs such as haloperidol; the adjusted odds ratios for current use were 24.1 (95% CI 3.3 – 172.7) and 3.3 (95% CI 0.8 – 13.2) respectively. The study was confined to patients who had received at least one prescription for an antipsychotic drug as an outpatient at some time during a nine-year period; this provided some control for the underlying conditions for which patients are prescribed these drugs and for surveillance bias. Unlike the study of clozapine users, the reasons for which patients took antipsychotic drugs in this study included medical, as well as, psychiatric conditions. None of these diagnoses were independently associated with an elevated risk of venous thromboembolism, which increases the likelihood that the drugs themselves were responsible for the increased risk.

The investigators also explored the risk of venous thromboembolism in current users of antidepressants; the unadjusted unmatched odds ratio was 1.7 (95% CI 0.8 – 3.7) (Zornberg and Jick 2000). This result, which was based on three exposed cases and 20 exposed controls, should be interpreted with caution. By design, the analysis included only those antidepressant users who had been prescribed antipsychotic drugs during the study period and the underlying characteristics of such people might be different from other antidepressant users.

Findings from a reanalysis of data from the Leiden Thrombophilia Study were also consistent with an elevated risk of venous thromboembolism in current users of antipsychotic drugs; four of 474 cases and none of the 474 controls used antipsychotic drugs in the year before the index date. Like the study based on the GPRD, people who received psychotropic drugs in hospital were not included in this study; an unspecified number of patients were excluded because they were general hospital or psychiatric inpatients at the time of enrolment. Moreover, 51 eligible cases declined to participate and another 19 were excluded because of psychiatric morbidity which was expected to impair involvement in the research. Hence, it is possible that the true proportion of antipsychotic users in the population-based sample of people with deep vein thrombosis was underestimated. The researchers also reviewed necropsy reports at the Leiden University Medical Center and found that 10 of 27 deaths from idiopathic pulmonary

embolism occurred in psychiatric patients, five of whom were known users of antipsychotic drugs.

The findings of a fourth study were less consistent. Using linked data from health care administrative databases, a Canadian cohort study compared the risk of venous thromboembolism in users of thyroid replacement hormones and users of two groups of psychotropic drugs: antipsychotics and antidepressants (Ray et al. 2002). In relation to antipsychotics, an increased risk was found for users of butyrophenones only (adjusted hazard ratio 1.43 [95% CI 1.18 – 1.74]). However, the study was confined to patients aged 65 years or more and diagnostic bias could not be ruled out since users of antipsychotics were older, were more likely to be living in long-term care facilities, and may have been more cognitively impaired than people taking thyroid replacement therapy. If venous thromboembolic events were less likely to have been recognised in such people, an increased risk in antipsychotic users might have been missed. Moreover, only those patients who were dispensed at least two prescriptions within 180 days of the initiation of treatment with one of the relevant drugs were included in the study. The duration of prescriptions was not stated, but assuming a one-month supply, this had the effect of excluding patients who took a medicine for just one or two months. It is more likely that the excluded patients were taking antipsychotic or antidepressant drugs than thyroid replacement therapy, since the latter treatment is usually taken without interruption. If, as suggested by the nested case-control study discussed above (Zornberg and Jick 2000), the risk of antipsychotic-related venous thromboembolism is greatest during the first few months of use, the exclusion of short-term users might have led to an underestimation of the true relative risk. No elevation of risk was found for antidepressant use. Two final points should be made about the design of this study. First, as the investigators conceded, they had very limited information about potential confounding factors and thus were unable to fully exclude confounding as an alternative explanation for their findings. Second, they inconsistently excluded patients who took warfarin or were diagnosed with cancer — those in whom the events occurred before the study period were excluded, whereas those that occurred after entry into a cohort were not.

Since the early years of their use through to the present day, antipsychotic drugs, especially phenothiazines, have also been implicated in sudden cardiac death (Kelly et

al. 1963; Hollister and Kosek 1965; Ray et al. 2001; Hennessy et al. 2002). Similarly, sudden deaths in users of tricyclic antidepressants have been attributed to cardiac causes (Mehtonen et al. 1991). Hence, it is possible that deaths from pulmonary embolism could be misclassified as myocardial infarction or arrhythmia-induced (and vice versa) when necropsies are not performed. For instance, in a recent case-control study, thioridazine was identified as a risk factor for sudden unexplained death among psychiatric inpatients (adjusted odds ratio 5.3 [95% CI 1.7 – 16.2]) (Reilly et al. 2002). Drug-induced arrhythmia was thought to be the most likely cause. Since a necropsy was performed in only 36% of cases, the possibility that some of the remaining patients died from pulmonary embolism cannot be ruled out. Interestingly when the analysis was confined to patients who had undergone a necropsy, a significant association between thioridazine and sudden unexplained death was not found (adjusted odds ratio 2.9 [95% CI 0.7 – 11.7]).

3.3.3 Why might antipsychotic drug use increase the risk of venous thromboembolism?

It has been suggested that the characteristics of the people who use antipsychotic medicines, features of the underlying condition for which they are taken, or side effects of the drugs such as sedation-induced immobility and obesity might be responsible for the observed increased risk of venous thromboembolism in users of these drugs (Tapson 2000; Tipper et al. 2001). However, as already discussed, two of the analytical studies which found an elevated risk in current users took previous users as the reference group, which provides some evidence against the first two hypotheses (Walker et al. 1997; Zornberg and Jick 2000). Moreover, patients with major risk factors for venous thromboembolism were excluded from the nested case-control study, the relative risk estimates were adjusted for BMI and other potential confounding factors, and none of the cases were immobilised or acutely psychotic in the two months before the index date (Zornberg and Jick 2000).

At the time that these studies were published, several mechanisms had been proposed to explain the suspected association between antipsychotic use and venous thrombosis. First, it appeared that platelet aggregation was enhanced during treatment with such medicines (Boullin et al. 1975; Orr and Boullin 1976; Ruh-Bernhardt et al. 1976), although the results were not consistent (Boullin et al. 1978; Orr et al. 1981). Second, lupus anticoagulant and anticardiolipin antibodies, which are associated with an

increased risk of venous and arterial thromboembolism (Greaves 1999; Levine et al. 2002), had been observed in patients taking antipsychotic drugs (Zarrabi et al. 1979; Canoso and Sise 1982; Canoso et al. 1990; Davis et al. 1994), including users who suffered venous or arterial events (el-Mallakh et al. 1988; Steen and Ramsey-Goldman 1988; Roche-Bayard et al. 1990; Ducloux et al. 1999; Maynes 2000). However, these antiphospholipid antibodies had also been found in people with acute psychosis before the commencement of antipsychotic therapy (Chengappa et al. 1991; Schwartz et al. 1998) and in healthy individuals belonging to families with several schizophrenic members (Firer et al. 1994). Moreover, some research had suggested that, unlike the antiphospholipid antibodies associated with systemic lupus erythematosus and other autoimmune conditions, antipsychotic-induced antibodies did not seem to carry the same, or any, risk of venous (Canoso and de Oliveira 1988; el-Mallakh et al. 1988) or arterial (Metzer et al. 1994) thromboembolism.

Other suggested mechanisms to explain the association included the exacerbation of venous stasis during sedation (Zornberg and Jick 2000), increased adrenaline secretion during the acute psychotic phase (Hindersin et al. 1984), and the increase in homocysteine levels found in some schizophrenics (Susser et al. 1998).

3.3.4 Summary

In stark contrast to the huge volume of research on oral contraceptive safety, the risk of venous thromboembolism in users of antipsychotics has been poorly investigated. More than fifty years after the emergence of the first case reports of venous thromboembolism in users of antipsychotic drugs, information from analytical epidemiological studies is limited. Nonetheless, the data from two well-designed studies are suggestive of a causal relationship between antipsychotic use and venous thromboembolism (Walker et al. 1997; Zornberg and Jick 2000); in both studies the drug exposure clearly preceded the thrombotic event, the relative risk estimates were high (especially for low potency conventional antipsychotics), the association was apparent in two different populations using two different study designs, an elevated risk was found for both fatal and non-fatal events, and some biologically plausible mechanisms by which antipsychotic drugs might increase the risk of venous thromboembolism have been proposed.

While there have been case reports of venous thromboembolism in users of antidepressants, it is unclear whether an association exists.

CHAPTER 4 CASE-CONTROL STUDY OF THE USE OF ORAL CONTRACEPTIVES AND PSYCHOTROPIC DRUGS: OBJECTIVES AND METHODS

4.1 INTRODUCTION

4.1.1 Oral contraceptives and venous thromboembolism

As discussed in the previous chapter, the risk of venous thromboembolism in women taking oral contraceptives containing desogestrel or gestodene appears to be about double that of women using levonorgestrel formulations. Although the absolute risks are not high, the excess risk has been of particular concern in New Zealand because of the extensive use of these oral contraceptives. At the time of the CSM warning in October 1995, almost 80% of oral contraceptive users in New Zealand were taking a preparation containing desogestrel or gestodene (Wilson 1999), which represented the highest proportionate use among countries for which utilisation data were available (Paul 1996). Indeed, these pills had been promoted to New Zealand doctors as the preferred choice for women requiring oral contraceptives (Bagshaw 1992). Based on the number of women taking desogestrel and gestodene contraceptives in New Zealand in 1995, it was estimated that 20 cases of venous thromboembolism among pill users would be prevented each year if older preparations were used instead (Paul 1996).

The regulatory response by the New Zealand Ministry of Health to this issue was described by the Chair of the New Zealand Medicines Adverse Reactions Committee as "muted" (Maling 1999). As outlined in the previous chapter, the Ministry's immediate response to the CSM announcement was to recommend that women at high risk of venous thromboembolism should consider using contraceptives other than desogestrel and gestodene preparations (Paul 1996). This advice was retracted a week later, pending the release and peer review of the key studies. In February 1996, following the publication of these studies, the Ministry sent New Zealand doctors a summary of the results and recommended that they "include this information on the relative risk of venous thromboembolism in the discussion of relative risks and benefits of contraceptive methods" (Medsafe 1996a). The communication concluded with the advice that until other potential risks and benefits of desogestrel and gestodene contraceptives were clarified there was "no sound basis for recommending any change

to current contraceptive practices". However, the Medicines Adverse Reactions Committee disagreed with this position. In March 1996, after reviewing the published data, the Committee urged the Ministry to recommend a change to prescribing practices as soon as possible (Aggett 1997). The key recommendations of the Committee, which were based on guidelines issued by the Faculty of Family Planning and Reproductive Health Care of the Royal College of Obstetricians and Gynaecologists in the UK (Mills et al. 1996), were that older low-dose pills should be *preferentially* prescribed to women starting on oral contraceptives, and that women with risk factors for venous thromboembolism who were already using desogestrel or gestodene preparations should be changed to other products (Aggett 1996).

However, the new recommendations were not released until July 1996 and they were less directive than those originally proposed by the Medicines Adverse Reactions Committee (Paul 1996). In brief, doctors were advised that *consideration* should be given to prescribing oral contraceptives other than desogestrel and gestodene preparations when initiating oral contraceptive therapy (Medsafe 1996b). In addition, various circumstances were outlined in which current users of such pills should be changed to another oral contraceptive preparation, or to a different method of contraception altogether. The tempering of the advice from the Medicines Adverse Reactions Committee and the delay in its release was due, in part, to pressure from the Royal New Zealand College of Obstetricians and Gynaecologists, the General Practitioners Association, and the New Zealand Family Planning Association, who were apparently concerned that the original advice would create a pill scare (Aggett 1997; Maling 1999). In addition, at least one pharmaceutical company threatened legal action after industry representatives were shown drafts of the proposed advice.

Unfortunately, during the hiatus between the publication of the key studies and the release of the prescribing recommendations in July 1996, New Zealand doctors were exposed to misleading interpretations of the data by the pharmaceutical industry and the Family Planning Association (Paul 1996). In fact, for several years a spokeswoman for the latter organisation continued to cite various biases as explanations for at least some of the excess risk of venous thromboembolism in users of desogestrel and gestodene contraceptives (Roke 1997a; Roke 1997b; Roke 1998; Roke 1999; Egermayer and Roke 2000). The data were also misrepresented by the New Zealand branch of the Royal

Australian and New Zealand College of Obstetricians and Gynaecologists, which asserted in 2000 that there was no evidence that desogestrel and gestodene oral contraceptives carried a higher risk of venous thromboembolism than older preparations (New Zealand Committee RANZCOG 2000). The information on which this statement was based appeared to have been provided to the authors at a pharmaceutical industry-sponsored meeting in Hong Kong, at which investigators from the Transnational and MediPlus studies were invited speakers (Skegg 2000a)

These influences might partly explain why the release of the Ministry's advice in July 1996 had a very modest impact on prescribing practices. In 1998, the proportion of oral contraceptive users taking desogestrel or gestodene preparations was still about 62% (Wilson 1999). In contrast, the proportion plummeted to around 30% in the wake of adverse media publicity at the beginning of 1999 about the unexpectedly high number of deaths from pulmonary embolism in users of desogestrel and gestodene contraceptives (Egermayer 1999). Based on the prevalence of use of these pills in New Zealand women during the mid-1990s, and on estimates of venous thromboembolism incidence and case-fatality, one death from pulmonary embolism among users would have been expected every 1.5 to 2.5 years (Medsafe 1998). However, the Centre for Adverse Reactions Monitoring had received spontaneous reports of six deaths in women taking desogestrel or gestodene contraceptives between January 1993 and June 1998, four of which had occurred during the 18 months to June 1998 (Medsafe 1998).

The present study of oral contraceptive use and fatal pulmonary embolism was prompted in part by this apparent excess number of deaths and in part by the lack of information about oral contraceptive use and the risk of *fatal* venous thromboembolism, especially within populations where desogestrel and gestodene contraceptives were widely used. At the time the present research was initiated only two case-control studies had investigated the risk of fatal pulmonary embolism in relation to oral contraceptive use. The first was conducted in the UK during 1966, well before the development of desogestrel and gestodene contraceptives (Inman and Vessey 1968). Using data presented in the paper, a crude odds ratio of 7.7 for current use of oral contraceptives can be derived. The second study examined deaths in England and Wales between 1986 and 1988, and it is likely to have included few users of desogestrel and gestodene pills (Thorogood et al. 1992b). In this case-control study based on 60

cases aged 16 – 39 years and 115 age-matched controls selected from the same general practices as the cases, the odds ratio for fatal pulmonary embolism among women who had used oral contraceptives in the preceding month was 2.1 (95% CI 0.8 – 5.2). The only study to contain specific information about fatal venous thromboembolism and desogestrel and gestodene contraceptives was the GPRD study undertaken by the Boston group in which there were only six deaths from pulmonary embolism among oral contraceptive users (Jick et al. 1995).

The final impetus for undertaking the present research was the potential for addressing some of the concerns voiced by the critics of the key studies. For example, referral and diagnostic biases would be highly unlikely in a study of fatal events. Moreover, in a relatively geographically isolated island nation such as New Zealand it would be possible to include all cases that occurred in the population.

4.1.2 Psychotropic drugs and venous thromboembolism

As outlined in the previous chapter, there is little information from analytical epidemiological studies about psychotropic drug use and venous thromboembolism. The data about fatal events are even more limited — the only study to have quantified the risk of fatal pulmonary embolism in users of antipsychotics was confined to an atypical preparation, clozapine (Walker et al. 1997). The present research was therefore undertaken to explore the risk of fatal pulmonary embolism in users of psychotropic drugs.

4.2 OBJECTIVES

The objectives of the study were as follows:

1. To examine any association between the use of oral contraceptives and the risk of fatal pulmonary embolism
2. To estimate the absolute risk of fatal pulmonary embolism in users of oral contraceptives

3. To assess the completeness of reporting of cases of fatal pulmonary embolism involving the use of oral contraceptives to the Centre for Adverse Reactions Monitoring
4. To explore any association between the use of antipsychotic and other psychotropic drugs and the risk of dying from pulmonary embolism.

4.3 DEFINITIONS

As discussed in Chapter 2, the date of onset of the fatal episode was taken as an index date. Cases and controls were defined as ever users of a medicine if their medical records indicated that they had been given a prescription for that medicine at any time before the index date. Because of the way in which oral contraceptives were packaged during the study period, the minimum amount that could be prescribed at any one time was a one-month supply. Hence, the use of oral contraceptives was defined, indirectly, as prescribed use of at least a month's duration. For different reasons, the use of psychotropic drugs was also defined as prescribed use of at least a month. The rationale for this definition was that psychotropic drugs are sometimes prescribed in one-off doses or very short courses (for example, to treat conditions such as nausea and insomnia) and it was decided that the inclusion of such brief episodes of treatment might dilute any true increased risk of venous thromboembolism in users of these medicines.

Current use of a medicine was defined as prescribed use at any time during the three months before the index date. Under this definition if a prescription was issued before the relevant three-month interval, but the duration of the prescribed course was such that it continued into that period, such use was classified as current.

Oral contraceptives were classified according to whether they contained the so-called third generation progestogens (desogestrel and gestodene), levonorgestrel, or cyproterone acetate. Hormone replacement therapy was categorised as oestrogen-only, combined (oestrogen and progestogen) continuous, and combined sequential. Psychotropic drugs were divided into three groups: antipsychotics, antidepressants, and other psychotropics (a group including benzodiazepines and other anxiolytics, lithium

carbonate, carbamazepine, sodium valproate, and zopiclone). The antipsychotic agents were classified according to potency, that is, the dose of the drug required to achieve a therapeutic effect (Zirkle and Kaiser 1974; Davis 1976; Zornberg and Jick 2000; Bourne and von Zastrow 2001; Potter and Hollister 2001a)

Women aged 15 – 49 years were classified as being of child-bearing age and hence potential users of oral contraceptives. Women of any age were defined as post-menopausal if there was a clear statement in the medical records that they had reached the menopause. If menstruation had ceased because of surgery, chemotherapy, or radiation, menopause was classified as artificial; otherwise it was categorised as natural.

4.4 METHODS

4.4.1 Overview

This was a records-based case-control study in which the controls were randomly selected from the same general practices to which the cases had belonged on the index date. Information about medicine use and other risk factors for venous thromboembolism was abstracted from the records of general practitioners, family planning clinics, and psychiatric services, using an identical approach for cases and controls. The following sections provide a more detailed account of these procedures.

4.4.2 Ascertainment of cases

The methods used to identify all men and women aged 15 – 59 years who died in New Zealand between 1 January 1990 and 31 December 2000, for whom the underlying cause of death was pulmonary embolism, were described in Chapter 2. At the time that the present case-control study was initiated, mortality data were not available for deaths that occurred in 1999 and 2000. Hence, the study was based on people who died between 1 January 1990 and 31 December 1998. Only those who were normally resident in New Zealand on the index date were eligible for inclusion (n=92).

Overseas visitors were excluded from the study for several reasons. First it would have been difficult to find an appropriate comparison group for the people who died while visiting New Zealand, since such people may have differed from New Zealand residents

with respect to their background risks of venous thromboembolism and other factors. Second, the prescribing practices in the countries in which these people normally resided may have differed from those encountered in New Zealand. Third, it was unlikely that general practitioner and other medical records could be obtained for people who were not normally resident in New Zealand.

To explore the association between oral contraceptives and fatal pulmonary embolism, the analysis was restricted to pre-menopausal women aged 15 – 49 years. In 2000, the results of an analysis based on deaths between January 1990 and August 1998 were published (Parkin et al. 2000). Subsequently, information about deaths that occurred in the final months of 1998 became available, and these women ($n=4$) were included in the present analysis. Another woman, who died in 1993, was also included after it was found that her date of birth had been incorrectly recorded in the data supplied by the New Zealand Health Information Service and that she was aged 49 years on the index date.

4.4.3 Arranging general practice visits

The methods used to identify the general practitioners of the cases were outlined in Chapter 2. For two cases (who died in 1992 and 1993), the name of the general practitioner was not found. Thus, for the present case-control study, the general practitioners of 90 of the 92 eligible cases were sent letters about the study. As described in Chapter 2, these letters outlined the aims of the research and requested permission for me to visit the practice to examine the records of the case and four randomly selected controls (Appendix A, letters 15 and 16). The general practitioner was subsequently telephoned, further information about the study was provided, and an appointment was made for a visit. At this time, an enquiry was also made about the existence of any family planning clinics in the local area. This supplemented the information already provided by the Family Planning Association about the clinics they operated.

No doctor refused to participate in the research, although six practices were not visited because the records had been destroyed (four cases) or lost (two cases) (see Table 2.5). The records of a further nine cases were not found when their respective general practices were visited. Hence, the general practice records of 75 eligible cases were

examined. The diagnosis of pulmonary embolism was confirmed by necropsy in 69, by ventilation-perfusion scans or angiography in three, and by the two specialists in internal medicine using standard criteria (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995a) in three.

4.4.4 Selection of controls

Eligibility criteria

For each eligible case four controls, matched by sex and year of birth, were selected from the general practice to which the case had belonged on the index date. For all but 13 cases (who had attended practices in which there was just one doctor), controls were selected from the group, rather than individual, medical practice. Potential controls were excluded if they were not normally resident in New Zealand, or were not members of the group practice, on the index date. Patients were regarded as belonging to the practice on the index date if they had a record of at least one consultation during the two years before that date. Selected persons who did not meet the eligibility criteria, and those whose records had been lost or transferred to another practice, were replaced.

The group, rather than the individual, general practice was chosen as a sampling frame to minimise any potential overmatching with respect to prescribing practices. It was thought that if such a phenomenon did occur, it would be most likely to arise in relation to the type of oral contraceptives that individual doctors chose to prescribe and would have the effect of biasing the odds ratio towards the null value. In any event, only six female cases aged 15 – 49 years belonged to sole-practitioner practices.

Of the 300 controls who were included in the study, 14 were born in adjacent (rather than the same) years to their case. There were three reasons for this. First, four small practices (each with either one or two general practitioners) had insufficient patients born in the appropriate years. Second, the year of birth recorded in the general practice records of one woman was a year later than the date recorded in the coroner's file and other official death records. Unfortunately this inconsistency was not noticed at the time of the practice visit and hence the year of birth that was used to select the controls for this case was incorrect. Third, one case had been a senior army officer and his primary medical care was provided by the New Zealand Army. It was therefore considered that the army health service should be considered his "general practice" and

that his controls should be men who had also received medical care from that service. However, because this man was middle-aged when he died during the early part of the study period, there were almost no men who were born in the appropriate year who were still serving in the New Zealand Army when the study was initiated. In particular, there were none in the military camp at which the case had been based when he died. Hence, to select controls, it was necessary to travel to the national facility where the medical records of all retired military personnel were stored. This facility contained the alphabetically filed records of men and women who had served in the New Zealand Army, Navy, or Air Force, as well as those who had undertaken compulsory military training. As some of the medical records dated back more than a century, it was not practicable to search these records to identify eligible controls. Instead, an index card system that contained demographic data for all military discharges after 1980 was examined. However, after several hours of searching, only one eligible control (a man who was born in the same year as the case and who was in the army on the index date) had been identified. Fortunately, three other men had been found who, although they were born in adjacent years to the case, were also in the army at the appropriate time. For pragmatic reasons, it was decided to include these men as controls.

Selection of controls from general practices with age-sex registers

For 71 cases, controls were selected from age-sex registers which were electronic in all but one practice. At the latter practice, the two general practitioners each had a paper-based register that was organised by year of birth. To randomly select four controls from these paper registers, a numbered list was compiled of women who were born in the appropriate year and a random numbers table (Lindley and Muller 1971) was used to select four. The medical records of those selected were then examined to determine whether they had been members of the practice on the index date. Since one of the selected patients did not belong to the practice on that date, the next random number in the sequence was used to select a fifth patient and so on, until a fourth eligible control had been identified.

At the time that the present study was initiated, most general practices were being run as private businesses and there was no requirement that they have electronic age-sex registers, let alone that they operate a particular brand of computer software. Hence, it was not surprising to find that a variety of software systems were being used in the 70

practices with electronic age-sex registers. These are listed in Table 4.1. Each software system had a search function that enabled a list of current and past (deceased and transferred) patients of the appropriate sex and year of birth to be generated. With some software this was a straightforward process, but with others it was not. For example, although a few systems allowed a direct search by year of birth (Medtech 32, Alumni, and two Others), most required a two-stage process of searching by age and then excluding those who were born in the adjacent year to the one of interest (GPDAT, MMAS, Medtech 16, Good Practice, Medcen, Houston, Profile for Mac, and one Other). When necessary, general practice and software company staff provided technical help with the searches.

Once a list of patients of the correct sex and year of birth had been compiled, those listed were numbered from one to 'n', and the random numbers table (Lindley and Muller 1971) was used to randomly select four. In some practices, it was possible to determine the date on which selected patients had joined the practice without examining the clinical records. In others it was necessary to look at the records, but the only information sought during this process related to demographic data and the dates of consultations. To ensure that the exposure status of potential controls remained unknown, the consultations notes were not read at this time. Any patients who were found to be ineligible were replaced by the patient corresponding to the next random number in the table.

Two doctors at different group practices (with two and six general practitioners respectively), would not allow their patients to be listed for potential selection. The sampling frame at all other group practices included the patients of all the doctors.

Table 4.1 Software used by practices with electronic age-sex registers

Name of software	Number of practices using this software
Alumni	6
Good Practice	2
GPDAT	11
MMAS	2
Houston	9
Medcen	2
Medtech 16	9
Medtech 32	22
Profile for Mac	4
Other	3
Total	**70**

Selection of controls from general practices without age-sex registers

The general practices of four cases did not have age-sex registers from which potential controls could easily be selected. The first of these was the "general practice" of the soldier for whom the methods used to select the controls are described above. At the second practice, the sole practitioner was asked to indicate where the records of the case would have been held, and a search was conducted through the adjacent records in both directions until four eligible controls were found. During this selection process, the records were examined only to obtain demographic data and the dates of consultations.

At the third practice, a university student health service, the records of former patients were archived by the latest year in which they had been registered as patients. Because the case was only in her second year of study when she died in 1993, it was decided not to select all of her controls from the files of students who had left the university during 1993 since this would have resulted in a potentially biased sample of students (those who had begun and completed their degrees exceptionally early, those who had left university without completing their course of study, and those who had died). Therefore, a search was made of the records of those students whose last year of registration was 1993, 1994, 1995, and 1996, and one eligible control was selected from each of these years using the method described for the solo practice above.

The practice which had been abandoned and placed into receivership (see Chapter 2) was the fourth practice for which there was no age-sex register. The patient records from this practice were held in three different places: the two remaining general practices in the town and the receiver's storage shed. No eligible controls were found among the files held by the receiver. At one of the practices (run by a sole practitioner) it was possible to search for potential controls using an electronic age-sex register (Houston software), but none of the identified patients of the appropriate age and sex had been patients of the abandoned practice. The other practice in the town had a box of transfer forms, completed by former patients of the relevant practice, and this was searched to identify men who were born in the same year as the case. Exactly four were found and an examination of their medical files confirmed that they had all been members of the practice on the index date.

In summary then, the controls were selected randomly from an age-sex register in 71 practices (electronic in all except one), from patient registration slips in one practice, and by random selection of medical records in three practices.

4.4.5 Information obtained from general practice records

As described in Chapter 2, information about medical histories and drug exposures before the index date was abstracted from the records (including any electronic records) of general practitioners and recorded on a standardised data form (Appendix B), using an identical approach for cases and controls. The assistance of general practitioners was sought only if required to decipher the notes. Only information that had been recorded before the index date was used to compare cases and controls.

All data abstraction forms were labelled with a study identification number, rather than the name of the case or control, and the key which linked names with identification numbers was stored separately from the forms. The sex and date of birth of each person was recorded, as was the date on which they had joined their general practice. Because the records of 23 cases and 84 controls included information from practices to which they had previously belonged, the date of the earliest information was also noted so that any systematic difference in the total period of time during which information had been recorded for cases and controls could be identified.

Detailed information about the use of medicines before the index date was recorded on the data form. For women, this included any current or past use of oral contraceptives, other contraceptive methods, and hormone replacement therapy. Specifically, the documented use (yes or no) of each of the available contraceptive methods in the year before the index date, and at any time before that year, were recorded. The details of each prescription for oral contraceptives (date, brand, duration of supply) were then noted, as were the details of all contraceptive methods used in the year before the index date (date, method, brand, duration of supply). For hormone replacement therapy, the date, regimen, and duration of all prescriptions were recorded.

For both men and women, the particulars (date, medicine, dose, frequency, duration of supply) of all other medicines that were prescribed in the year before the index date were noted. The use of any psychotropic drugs before that year was also recorded.

In addition, the presence (including details) or absence of any documented history of the following were recorded: medical conditions associated with an increased risk of venous thromboembolism (including a history of deep vein thrombosis or pulmonary embolism, superficial venous thrombosis, varicose veins, known thrombophilia, systemic lupus erythematosus, inflammatory bowel disease, and malignancy); temporary risk factors for venous thromboembolism in the year before the index date (including major surgery, injury requiring medical attention, prolonged immobility, and pregnancy); other medical conditions (including ischaemic and other heart disease, stroke, transient ischaemic attacks, hypertension, diabetes, renal disease, and liver disease); intellectual disability; menopause (including the date of the last menstrual period and whether the menopause was natural or artificial); and a family history of venous thromboembolism. Details of all documented pregnancies were recorded, as were the most recently recorded smoking status, weight, and height (including narrative comments). The ethnicity of cases and controls, when documented, was also noted.

4.4.6 Family planning clinic visits

For the reasons outlined in Chapter 2, permission was sought and obtained to examine any family planning clinic records that existed for female cases and controls. Once a time had been made to visit the general practitioner of a female case, the local family planning clinics (if any) were contacted by telephone and arrangements for viewing any records were discussed. At this stage it was possible to supply the name and date of birth of the case, but obviously not those of her controls who were yet to be selected. On the day of the general practice visit, the family planning clinics were contacted as soon as four eligible controls had been identified. If records were found for any of the women, the clinic was then visited and information was abstracted using an identical data form to that employed during the general practice visit. In all, four cases and 17 controls had family planning clinic records.

4.4.7 Examination of mental health records

The general practice records of three patients (all cases) indicated that they were being prescribed psychotropic drugs by a psychiatrist, but the specific details of their treatment were not recorded. For these patients, the psychiatric records were examined in order to confirm the type and dose of medicine being taken.

4.4.8 Data management

Coding and data entry

The information recorded on the data abstraction forms was numerically coded using a data dictionary (Appendix B). A simple draft version of this dictionary was developed before the data were collected, although decisions about how to code some of the more detailed information were not made until all the information had been obtained. As will be discussed below, some additions to the dictionary were required because of the incomplete nature of some information (for example, the dates on which conditions were diagnosed and the duration of prescriptions for contraceptives).

The information from each data form was coded and entered into Excel spreadsheets by a research assistant and me, working independently of each other. If two data abstraction forms existed for a female case or control (because she had visited a family planning clinic as well as her general practitioner), the information was merged to create one record. The same approach was taken for the prescription data obtained from psychiatric services.

Although every documented prescription for oral contraceptives was recorded on the data abstraction form, this information was summarised by entering it into the spreadsheet as episodes of continuous use. Such episodes were defined as those in which consecutive prescriptions for a particular preparation were issued, provided that any interval occurring between the date on which the supply from one prescription would have run out, and the start date of the next, was less than three months. This interval was chosen to be consistent with the assumption underlying the definition of current oral contraceptive use — that is, that the increase in venous thromboembolism risk might persist for up to three months following discontinuation of use. The start date of an episode of continuous use was taken as the date of the first prescription; the end date was calculated using the date of the final prescription and adding the number of months prescribed on that occasion. If the end date was less than three months before the index date, or the supply would have lasted beyond the index date, the woman was coded as a current user.

There were a few situations in which the information about oral contraceptive use was incomplete. These situations, and the rules established to deal with them in a consistent manner, are as follows:

1. *The medical practitioner had recorded the date on which a prescription had been issued, but not the amount prescribed.*

   Normally, users of oral contraceptives are given a three or six-month supply, since one box of pills contains three one-month blister packs. Therefore, if the duration of a particular prescription was unknown, but there was an obvious precedent of prescribing a three or six-month supply, then it was assumed that the same amount had been prescribed on this occasion. If no obvious precedent existed and no subsequent prescriptions were provided, it was conservatively assumed that a three-month supply had been prescribed. Rarely, the provision of a six, rather than three, month supply would have made a difference as to whether or not a woman was classified as a current user (or a user in the year before the index date). In these situations the uncertainty regarding the end date of the episode of use was flagged by coding the woman as a possible current user (or a possible user in the year before the index date).

2. *A woman became pregnant while apparently taking an oral contraceptive.* In the absence of any other information, the end date of the episode of contraceptive use was taken as the date of the pregnancy test. If that date was not recorded, the date five weeks after the last menstrual period was taken.

3. *A woman's medical records indicated that she had used oral contraceptives in the past, but full details were not provided.*

   If the start and end dates of these episodes had been coded as unknown, then any information that was available about the calendar year or duration of use would have been lost. Two "extra data" columns were therefore created in which to record this information. If, for example, the medical practitioner had recorded in November 1997 that a woman was taking an oral contraceptive but there was no subsequent mention of use, "November 1997" was recorded in both of the extra data columns. Similarly, if a doctor recorded in April 1992 that a woman had

taken the pill for six months in the past, then "six months" was recorded in the first extra data column and "pre-April 1992" was recorded in the second.

For other methods of contraception, information about use during three time periods was coded — before the year of interest, at any time during the year before the index date, and during the three months before the index date.

Hormone replacement therapy was also summarised as episodes of continuous use. Unlike oral contraceptives, no more than a three-month supply of hormone replacement therapy could be issued on one prescription during the study period. Hence, the coding proved relatively straightforward.

A copy of a drug dictionary devised and used by the New Zealand Centre for Adverse Reactions Monitoring was used to assign numerical codes to other medicines taken in the year before the index date. These codes comprised a prefix and suffix, which together identified individual medicines. Moreover, the prefix allowed medicines to be identified by pharmacological group. The clinical indication for which each medicine was prescribed was also coded, as was the presence or absence of current use.

Because information about the dates on which medical conditions were first diagnosed or treated was sometimes incomplete, the following coding conventions were established:

1. If the month and year only were recorded, the date was taken as the fifteenth day of that month and year.
2. If the year only was recorded, the date was taken as 1 July of that year.
3. If the decade only was recorded, the date was taken as 1 July of the fifth year during that decade.
4. If the age of a patient was recorded, rather than a date, the date of diagnosis or treatment was taken as the date six months after the date that the patient turned that age. For example, if the records stated that a patient was diagnosed with a condition aged 33 years, then the date on which that person had lived for 33.5 years was taken as the date of diagnosis.

5. Some doctors had noted that their patient had been diagnosed with a condition sometime in the past, but the date of diagnosis was not documented. In this situation, the date on which the information was recorded was entered into the spreadsheet and the fact that the diagnosis was made sometime before this date was flagged by entering the numeric value "1" in an associated date indicator box.

Checking the data

To check for coding and data entry errors, the separate spreadsheets compiled by the research assistant and me were compared using a computer programme written by Mr Peter Herbison, a biostatistician in the Department of Preventive and Social Medicine. Any inconsistencies between the two spreadsheets were resolved by consensus after referring to the original data abstraction forms.

Preliminary analysis

Following the steps described above, the data were imported into the SPSS statistical package (version 6.1.4). Several new variables were created from the coded data. For currently used medicines, the new variables (with their categories in parentheses) were as follows: the progestogen contained in oral contraceptives (levonorgestrel / desogestrel or gestodene / cyproterone acetate), the hormone replacement therapy regimen (oestrogen-only / sequential combined / continuous combined), the type of psychotropic (any / antipsychotic / antidepressant / other), and the type of antipsychotic (low potency / high potency). Variables were also produced for these medicines to indicate ever use (use at any time before the index date), past use (use before, and excluding, the three months before the index date), never use, and use in the month before the index date.

In addition, variables were generated to indicate a history of the following: at least one live birth, breast cancer, and the presence of a chronic musculoskeletal condition that might have affected mobility in the two months before the index date.

Summary weight variables were created after converting imperial measurements for weight or height to the metric scale. In the first of these variables, three categories of measured weight (low, medium, and high) were defined based on the weight

distribution of the controls. A second weight variable, which included both comments and measured weight, was derived by assigning people for whom a comment about weight had been made to one of the above categories as appropriate. A third variable was created by dividing measured weight into two groups based on the median weight of the cases. Each of the three weight variables included a category for missing values.

Finally, simple frequencies for all variables were produced and the following means were computed for cases and controls: age on the index date, number of years spent as a member of the general practice, number of years of years spent as a member of the practice by history of mental illness, number of years of recorded information, weight, and height. The t-test for equality of means was used to calculate the p-value for any differences. The data were then transferred to STATA (version 7.0) in order to undertake matched analyses using conditional logistic regression.

4.4.9 Statistical analysis

The following logistic regression analyses were undertaken by Mr Peter Herbison, in collaboration with me.

Analyses involving oral contraceptives

To explore the association between the current use of oral contraceptives and fatal pulmonary embolism, the key analyses were restricted to pre-menopausal women who did not have a history of venous thromboembolism. Analyses were also undertaken from which women were excluded if they had a history of pregnancy or prolonged immobility during the two months before the index date. There were no women aged 15 – 49 years who had a major injury or surgery during the same period.

Non-users of any oral contraceptives in the three months before the index date were taken as the reference group. This group therefore included both never users and past users. The association was explored for four categories of oral contraceptives according to the progestogen that they contained: any, levonorgestrel, desogestrel or gestodene, and cyproterone acetate.

As the study employed a matched design, a matched analysis was undertaken using conditional logistic regression. However, unstable estimates were obtained because of

sparse data. This problem was clearly illustrated by undertaking a stratified analysis using the method of Mantel and Haenszel (Mantel and Haenszel 1959): each matched set was treated as a separate stratum and a summary odds ratio was estimated for current use of any oral contraceptive. Eight of 29 strata contributed no information to this odds ratio because the exposure status was concordant (the case and all four of her controls were exposed to an oral contraceptive [one stratum] or neither the case nor any of her controls were exposed [seven strata]). This loss of information was exacerbated in analyses which explored the association by category of oral contraceptive, and occurred in strata where:

1. The case was a user of an oral contraceptive, but was not taking a preparation from the category of interest, and some or none of the controls were users of contraceptives in that category.
2. The case was a non-user, and although some or all of the controls were users of an oral contraceptive, none were users of the preparations from the category of interest.

The main purpose of matching is to permit the use of efficient analytical methods to control for confounding by the matching factors (Breslow and Day 1980). However, as was found in the present study, it can also result in a considerable loss of information that can harm efficiency (Rothman and Greenland 1998). Since matching forces the controls to be more similar to cases with respect to exposure than they would otherwise have been, a matched design requires that the matching be taken into account in the analysis otherwise the risk estimate will be biased towards the null value (Breslow and Day 1980; Rothman and Greenland 1998). It follows that an unmatched analysis can be undertaken provided that the matching factors are adjusted for in the analysis. Hence, in the present study, to explore the association between oral contraceptive use and pulmonary embolism an unmatched analysis was undertaken using unconditional logistic regression, while adjustment was made for age as a continuous variable and the standard error was adjusted for clustering by general practice. Adjustment was also made for weight category (based on measured weight and comments), but because of the small numbers there was limited capacity to explore potential confounding by other risk factors for venous thromboembolism.

To determine the total woman-years of oral contraceptive use during the study period, contraceptive-supply data were obtained from the Ministry of Health. These data were obtained before the study was expanded to include deaths in the final quarter of 1998 and thus relate to use between 1 January 1990 and 31 August 1998. To estimate the absolute risk of dying from pulmonary embolism for current users of oral contraceptives, the number of deaths among users between these dates was divided by the total woman-years of use.

Analyses involving psychotropic drugs

Matched analyses, using conditional logistic regression, were undertaken to examine the association between categories of psychotropic drugs (antipsychotics, antidepressants and other) and fatal pulmonary embolism. To check the stability of the estimates thus produced, unconditional logistic regression analyses were also undertaken in which adjustment was made for the matching factors. The association between psychotropic drug use and fatal pulmonary embolism was examined for all subjects, although the key analyses were restricted to those without major risk factors for venous thromboembolism. The latter group is regarded as the most informative for studying adverse effects of medicines (Jick et al. 1998b).

All estimates were adjusted for weight category (based on measured weight and comments), and oral contraceptive use and hormone replacement therapy within three months of the index date. In the analyses which examined the association between antidepressants and pulmonary embolism, two approaches were employed to deal with concurrent use of antipsychotics. In the first, current users of antipsychotics were excluded from the analyses. In the second, the odds ratios were adjusted for such use.

4.4.10 Sample size calculations

Sample size calculations were undertaken using PS software (Dupont and Plummer 1998) for a matched case-control design with a case:control ratio of 1:4, alpha of 0.05, a correlation coefficient for failure of 0.01, and power of 80%.

Oral contraceptive analyses

Using the age-specific prevalence of oral contraceptive use estimated from a recent national survey (Pool et al. 1999) and the age distribution of female cases aged 15 – 49

years (and therefore of age-matched controls), the prevalence of exposure among the controls was estimated to be 19%. Pulmonary embolism was the underlying cause of death in 40 New Zealand women aged 15 – 49 years who died during the study period (1 January 1990 and 31 December 1998). Hence, assuming a prevalence of exposure of 19%, it was calculated that the study would have sufficient power to detect an odds ratio of 2.9 for current use of any oral contraceptive. It was anticipated, however, that several cases would be excluded from the key analyses because they were post-menopausal or they had major risk factors for venous thromboembolism. Moreover, because of media reports of proposed litigation against doctors who had prescribed desogestrel or gestodene oral contraceptives to women who had subsequently developed venous thromboembolism (MacKinven 1999), it was also thought that some general practitioners might decline to participate in the study. Therefore, the odds ratios which could be detected with fewer cases were also calculated as shown in Table 4.2.

Table 4.2 Number of cases required for the oral contraceptive analyses

Odds ratio	Number of cases required*
2.9	41
3.0	38
3.1	35
3.2	33
3.3	31
3.4	30
3.5	28
3.6	27
3.7	26
3.8	24
3.9	23
4.0	22

* Assuming a prevalence of exposure of 19% in the control group, a case:control ratio of 1:4, $\alpha = 0.05$, correlation coefficient for failure = 0.01, and power = 80%.

Psychotropic drug analyses

Based on the life-time prevalence of schizophrenia (Bromet and Fennig 1999), it was assumed that the prevalence of antipsychotic use was 1%. This was likely to be a conservative estimate because antipsychotic drugs are also used in the treatment of other conditions such as bipolar affective disorder. There were 92 New Zealand residents aged 15 – 59 years who died between 1990 and 1998 for whom the underlying cause of death was pulmonary embolism. Hence, assuming a prevalence of exposure of 1%, it was calculated that the study would have sufficient power to detect an odds ratio of 6.2. However, as in the sample size calculations for the oral contraceptive analyses, it was expected that some cases would be excluded from the key analyses because of pre-existing major risk factors for venous thromboembolism or the unavailability of records. Table 4.3 shows the odds ratios that could be detected with differing numbers of cases.

Table 4.3 Number of cases required for antipsychotic drug analyses

Odds ratio	Number of cases required*
6.0	98
6.1	95
6.2	92
6.3	90
6.4	87
6.5	85
6.6	83
6.7	80
6.8	78
6.9	76
7.0	75

* Assuming a prevalence of exposure of 1% in the control group, a case:control ratio of 1:4, $\alpha = 0.05$, correlation coefficient for failure = 0.01, and power = 80%.

4.4.11 Ethical matters

The principles of respect for autonomy and the minimisation of harm were observed in the design and conduct of this case-control study. Permission to examine the records of the cases and controls was obtained from general practitioners and family planning clinics, and (for mental health records) from senior medical advisors at the relevant hospitals. Individual patients were not approached for consent. Rule 11 of the Health Information Privacy Code (Privacy Commissioner 1994) and the Guidance Notes to the Code published by the Health Research Council of New Zealand (Health Research Council of New Zealand 1996) specify that disclosure of health information, without the authorisation of the individuals themselves, is lawful if it is either not desirable or not practicable to obtain this authorisation and the following two conditions are met:

1. The information is to be used for research purposes
2. The information will not be published in a form which could reasonably be expected to identify the individual concerned.

For deceased cases it was clearly not possible to obtain authorisation. Nor was it practicable to obtain authorisation before examining patient records in order to identify eligible controls. Once the controls had been selected, it remained impracticable to obtain individual consent because some of those chosen might have left the practice after the index date. If only those patients who could be traced and gave consent were included, the scientific validity of the study could have been compromised and the ethical status of the research threatened.

The information abstracted from the general practice, family planning, and mental health records was recorded without names and the data forms were stored in a locked filing cabinet. The key which linked the study identification numbers recorded on these forms with the names of the cases and controls was stored separately.

Ethical approval for the research was granted by each of the regional ethics committees.

CHAPTER 5 CASE-CONTROL STUDY OF THE USE OF ORAL CONTRACEPTIVES AND PSYCHOTROPIC DRUGS: RESULTS

5.1 SELECTION OF POTENTIAL CONTROLS AND THE AVAILABILITY OF THEIR GENERAL PRACTICE RECORDS

Of the 70 general practices which had electronic age-sex registers from which controls were selected, 54 had an electronic register on the index date. At these practices, all patients who had been members of the practice on the index date were included in the sampling frame, as well as people who had joined the practice after that date. This second group of patients was included in the sampling frame simply because the various software packages used by the practices did not permit the quick identification and exclusion of such people. In order to determine whether the patients who were selected as potential controls were, in fact, members of the practice on the index date, it was then necessary to examine their individual records. As can be seen in Table 5.1, the records of 46 of those selected had been lost or transferred to another practice and hence it was not possible to establish whether they would have been eligible for inclusion.

Sixteen general practices did not develop electronic age-sex registers until after the index date, as shown in Table 5.2. At some practices this meant that any potential controls who died or left the practice between the index date and the date on which the register was first compiled would not have been included in the sampling frame. At others, it is possible that such people could have been selected as potential controls because the details of all patients who had attended the practice in the past were retrospectively entered into the computer, although the approach to deceased patients varied. As shown in Table 5.3, it was not possible to examine the records of nine potential controls who were selected from the age-sex registers that were developed after the index date – although the true number of potential controls for whom records could not be examined is unknown for the reasons just described. Similarly, at the practices where controls were selected through random selection of patient records, it was not possible to quantify the number of potentially eligible patients who were not included.

Table 5.1 General practices which had an electronic age-sex register on the index date, numbers of potential controls for whom medical records were missing

Number of potential controls in practice for whom medical records were missing*	Number of practices	Number of missing records
0	35	0
1	8	8
2	4	8
3	4	12
4	2	8
10	1	10
Total	**54**	**46**

* Records lost or transferred to another practice.

Table 5.2 Number of years after index date that other practices first compiled an electronic age-sex register

Number of years after index date that register first compiled	Number of practices
< 1	-
1	2
2	5
3	3
4	3
5	2
Unknown	1
Total	**16**

Table 5.3 General practices which did not have an electronic age-sex register on the index date, number of potential controls for whom medical records were missing

Number of potential controls in practice for whom medical records were missing*	Number of practices
0	10
1	4
2	1
3	1
Total	**16**

* Records lost or transferred to another practice.

5.2 CHARACTERISTICS OF MALE AND FEMALE CASES AND CONTROLS AGED 15 – 59 YEARS

The demographic characteristics of the 75 cases for whom general practitioner records were found, and their controls, are shown in Table 5.4. Twenty-four of the cases included in the present case-control study were male and 51 were female. The female cases were younger than the male (median ages 43.0 years and 49.5 years respectively). The mean times that cases and controls had been members of their general practices were very similar (9.9 and 8.7 years respectively), as were the mean numbers of years of recorded medical information (13.5 and 12.2 years). Cases and controls who had a history of mental illness had been members of their respective practices slightly longer (10.3 and 11.5 years respectively) than cases and controls without such a history (9.7 and 8.3 years). Ethnicity was documented for only 16 (21.3%) cases and 54 (18%) controls.

Table 5.4 Demographic characteristics of cases and controls

	Cases (n=75)	Controls (n=300)
Sex (number [%])		
Male	24 (32.0)	96 (32.0)
Female	51 (68.0)	204 (68.0)
Age (years, median)		
All	45.0	45.0
Male	49.5	49.5
Female	43.0	43.0
Mean years in practice		
All	9.9	8.7
Male	10.5	9.5
Female	9.6	8.3
Mean years of recorded information		
All	13.5	12.2
Male	13.7	12.8
Female	13.4	11.9
Recorded ethnic group (number [%])		
European	15 (20.0)	30 (10.0)
Maori	-	10 (3.3)
Pacific Islands	1 (1.3)	10 (3.3)
Asian	-	4 (1.3)
Other	-	-
Not recorded	59 (78.7)	246 (82.0)

Other characteristics of cases and controls are shown in Table 5.5. Ten cases and two controls had a recorded history of venous thromboembolism. Six of these cases, and both controls, were diagnosed with deep vein thrombosis alone and the remaining four cases had objective evidence of pulmonary embolism. A history of superficial venous thrombosis and of varicose veins was also more common among cases. Two cases, and no controls, had a documented family history of venous thromboembolism. Cases were more likely than controls to have a history of a lower limb musculoskeletal condition that might have affected their mobility, acutely or chronically elevated platelet counts, a cardiac murmur of uncertain significance, peripheral vascular disease, and chronic renal disease. Eight cases had a documented intellectual disability, compared with just one control. Pregnancy-induced hypertension was more common among cases, although cases and controls had similar rates of hypertension that was unrelated to pregnancy. Six controls had a history of cancer, but none had an advanced malignancy. There were no cases with advanced cancer because such people did not meet the eligibility criteria for the study. Nor were there any cases with a history of cancer (that had apparently been cured).

Although doctors had recorded the weight of 54 (72.0%) cases and 209 (69.7%) controls before the index date, the files of only 28 (37.3%) cases and 59 (19.7%) controls contained a measurement of height. About half of the female (51.0%) and male (54.2%) cases belonged to the highest weight category (> 70 kg in females and 85 kg in males), compared with 27.0% and 17.7% of the female and male controls respectively.

Cases were more likely to have had major risk factors for venous thromboembolism in the two months before the index date. Five cases (two of whom had a history of venous thromboembolism) were confined to bed or a chair for more than a week. Two of these cases had also sustained a major injury. There were no controls who had been injured or immobilised during the same period. No cases or controls had a history of travel recorded in their general practice, family planning, or mental health records. Three controls were pregnant during the two months before the index date and two others had major surgery (one of whom had a history of venous thromboembolism).

Of those for whom smoking status had been recorded at some time before the index date, 59.2% of cases and 58.3% of controls were noted to be either current or past

smokers. Although similar proportions of cases and controls were prescribed medicines in the year before the index date, cases (62.7%) were more likely than controls (47.3%) to be current users of drugs other than contraceptives and hormone replacement therapy.

Table 5.5 Other characteristics of cases and controls

Characteristic	Cases (n=75)	Controls (n=300)
Recorded history (number [%])		
Venous thromboembolism	10 (13.3)	2 (0.07)
Superficial venous thrombosis	16 (21.3)	7 (2.3)
Varicose veins	14 (18.7)	24 (8.0)
Inflammatory bowel disease	1 (1.3)	1 (0.03)
Systemic lupus erythematosus	1 (1.3)	-
Hypertension unrelated to pregnancy	12 (16.0)	44 (14.7)
Angina	2 (2.7)	14 (4.7)
Myocardial infarction	1 (1.3)	5 (1.7)
Congestive heart failure	2 (2.7)	1 (0.03)
Stroke	1 (1.3)	-
Heart valve disease	-	3 (1.0)
Heart murmur, not otherwise specified	9 (12.0)	7 (2.3)
Cardiac conduction disorders	-	10 (3.3)
Palpitations, not otherwise specified	2 (2.7)	8 (2.7)
Peripheral vascular disease	3 (4.0)	2 (0.07)
Type I diabetes	-	1 (0.03)
Type II diabetes	2 (2.7)	8 (2.7)
Chronically elevated platelet count	4 (5.3)	1 (0.03)
Acutely elevated platelet count	4 (5.3)	4 (1.3)
Antiphospholipid syndrome	-	1 (0.03)
Chronic renal disease	3 (4.0)	2 (0.07)
Cancer	-	6 (2.0)
Intellectual disability	8 (10.7)	1 (0.3)
Musculoskeletal condition of lower limbs	9 (12.0)	11 (3.7)
Risk factors in 2 months before index date (number [%])		
Major injury	2 (2.7)	-
Prolonged immobility	5 (6.7)	-
Surgery	-	2 (0.07)
Pregnancy	-	3 (1.0)
Smoking status (number [%])		
Non-smoker	20 (40.8)	75 (41.7)
Smoker	18 (36.7)	69 (38.3)
Ex-smoker	11 (22.4)	36 (20.0)
Status not recorded	26 (34.7)	120 (40.0)

Characteristic		Cases (n=75)	Controls (n=300)
Pregnancy-induced hypertension (number [% female])		5 (9.8)	6 (2.9)
Weight category (number [% of sex])			
Females	Low (< 60 kg)	2 (3.9)	44 (21.6)
	Medium (60 – 70 kg)	10 (19.6)	48 (23.5)
	High (> 70 kg)	26 (51.0)	55 (27.0)
	Weight not measured	13 (25.5)*	57 (27.9)†
Males	Low (< 75 kg)	1 (4.2)	19 (19.8)
	Medium (75 – 85 kg)	2 (8.3)	26 (27.1)
	High (> 85 kg)	13 (54.2)	17 (17.7)
	Weight not measured	8 (33.3)	34 (35.4)‡
Prescribed medicines, excluding contraception and HRT (number [%])			
In year before index date		59 (78.7)	221 (73.7)
In 3 months before index date			
	Yes	47 (62.7)	142 (47.3)
	Possible	1 (4.2)	18 (6.0)
Recorded family history of venous thromboembolism (number [%])		2 (2.7)	-

* Comments in the records of two of these cases indicated that they were overweight.
† Comments in the records of three of these controls indicated that one was of average weight and two were overweight.
‡ Comments in the records of one of these controls indicated that he was overweight.

In unadjusted matched analyses (Table 5.6), significantly elevated risks of fatal pulmonary embolism were found for people with a history of venous thromboembolism, superficial venous thrombosis, varicose veins, pregnancy-induced hypertension, a chronic musculoskeletal condition of the lower limbs, and an intellectual disability. The relative risk estimates for all these factors were attenuated somewhat once people with a history of venous thromboembolism (and the controls of excluded cases) were excluded.

In an analysis based on the second weight variable described in the previous chapter (which classified people into weight categories on the basis of measurements or comments), people in the highest weight category and those for whom a record of weight was missing had a significantly greater risk of dying from pulmonary embolism than those in the lowest weight category. The point estimate for the highest weight category increased further in the analysis confined to people without a history of venous thromboembolism. Further analyses were undertaken in which measured weight was divided into two groups based on the median weight in cases (80 kg in women and 93 kg in men), rather than the tertiles which were based on the weight of controls. People whose weight was above the median, and those with missing values, had a greater risk of dying from pulmonary embolism than those whose weight was below or equal to the median.

Table 5.6 Various risk factors and fatal pulmonary embolism

Characteristic	Unadjusted matched odds ratios (95% CI), all subjects*	Unadjusted matched odds ratios (95% CI), subjects without a history of venous thromboembolism†
Recorded history		
Venous thromboembolism	37.6 (4.8 – 294.7)	-
Superficial venous thrombosis	14.3 (4.7 – 43.1)	9.3 (2.9 – 29.7)
Varicose veins	2.7 (1.3 – 5.7)	1.8 (0.8 – 4.3)
Pregnancy-induced hypertension	3.6 (1.0 – 12.7)	2.0 (0.5 – 8.7)
Intellectual disability	24.0 (2.9 – 199.3)	20.0 (2.3 – 171.2)
Musculoskeletal condition of lower limbs	3.6 (1.4 – 9.2)	2.9 (1.1 – 7.8)
Weight category‡		
Low	1.0	1.0
Medium§	3.2 (0.8 – 12.5)	3.3 (0.6 – 17.3)
High‖	12.8 (3.6 – 45.1)	15.8 (3.5 – 72.4)
Missing	4.9 (1.3 – 18.0)	6.9 (1.5 – 32.5)
Weight category based on median weight of cases¶		
≤ Median	1.0	1.0
> Median	5.4 (2.7 – 10.8)	6.6 (3.0 – 14.6)
Missing	1.7 (0.8 – 3.4)	2.1 (1.0 – 4.6)

* Based on 75 cases and 300 controls.
† Based on 65 cases and 259 controls.
‡ Based on measured weight and comments about weight. Females with measured weight of < 60 kg, 60 – 70 kg, and > 70 kg were classified as being of low, medium, and high weight respectively. For males the corresponding weight categories were < 75 kg, 75 – 85 kg, and > 85 kg respectively. One control for whom weight was not measured was assigned to the medium weight category, and two cases and three controls were assigned to the high weight category, on the basis of comments recorded in their medical records.
§ The control who was classified as being in the medium weight category on the basis of comments recorded in medical records is excluded from the second analysis because her case had a history of venous thromboembolism.
‖ One case who was classified as being in the high weight category on the basis of comments recorded in medical records is excluded from the second analysis because she had a history of venous thromboembolism.
¶ The median weight was 80 kg and 93 kg in female and male cases respectively.

5.3 ORAL CONTRACEPTIVES

5.3.1 Characteristics of female cases and controls aged 15 – 49 years

Thirty-three female cases were aged between 15 and 49 years on the index date; the median age of these cases (and their controls) was 33.0 years. The characteristics of this subset of cases and controls are shown in Table 5.7. Three cases had a history of venous thromboembolism, one of whom was also post-menopausal and had a history of prolonged immobility in the two months before the index date. A fourth case had spina bifida and was confined to a wheelchair. Three controls were pregnant in the three months before the index date and eight were post-menopausal. A further three controls may (according to the date of their last menstrual period) have been pregnant during the three months before the index date, but no information about the outcome of the pregnancy was recorded. There were no cases or controls who had suffered a major injury in the two months before the index date, and no controls who had been immobilised or undergone surgery. Fifteen (45.5%) cases either weighed more than 70 kg (*n=14*) or were noted to be overweight (*n=1*), as compared with 30 (22.7%) controls. Cases (54.5%) were more likely than controls (42.4%) to have taken medications other than contraceptives and hormone replacement therapy in the three months before the index date. Slightly smaller proportions of cases had ever been pregnant and had had at least one live birth.

Only one woman, a 48 year old control with hot flushes in whom menstruation had not ceased, was a current user of hormone replacement therapy (conjugated equine oestrogen 0.625mg and sequential medroxyprogesterone 10mg). Four other women (one case and three controls) had been prescribed hormone replacement therapy in the past. The case was prescribed an oral contraceptive followed by a six-week course of hormone replacement therapy about eighteen months before the index date to treat menorrhagia. One control was prescribed a three-month supply of hormone replacement therapy following a hysterectomy and oophorectomy two years before the index date. She was classified as being post-menopausal and was excluded from the key analyses. Another control was given a three-month course one year before the index date by a gynaecologist to treat break-through bleeding that was attributed to oral contraceptive pill-induced endometrial atrophy. She subsequently restarted the oral contraceptive pill and was a current user. The third control was prescribed a three-month course two years before the index date because of hot flushes and irregular

periods. Two months before the index date it was noted that she was continuing to menstruate.

Table 5.7 Characteristics of female cases aged 15 – 49 years

Characteristic	Cases (n=33)	Controls (n=132)
Recorded history (number [%])		
Venous thromboembolism	3 (9.0)	-
Superficial venous thrombosis	1 (3.0)	1 (0.8)
Varicose veins	2 (6.1)	4 (3.0)
Inflammatory bowel disease	-	-
Systemic lupus erythematosus	1 (3.0)	-
Hypertension unrelated to pregnancy	1 (3.0)	7 (5.3)
Pregnancy-induced hypertension	1 (3.0)	6 (4.5)
Angina	-	1 (0.8)
Myocardial infarction	-	1 (0.8)
Congestive heart failure	-	-
Stroke	-	-
Heart valve disease	-	1 (0.8)
Heart murmur, not otherwise specified	4 (12.1)	5 (3.8)
Cardiac conduction disorders	1 (3.0)	2 (1.5)
Palpitations, not otherwise specified	-	1 (0.8)
Peripheral vascular disease	2 (6.1)	1 (0.8)
Type I diabetes	-	1 (0.8)
Type II diabetes	1 (3.0)	1 (0.8)
Chronically elevated platelet count	3 (9.0)	-
Acutely elevated platelet count	1 (3.0)	2 (1.5)
Antiphospholipid syndrome	-	1 (0.8)
Chronic renal disease	2 (6.1)	2 (1.5)
Cancer	-	-
Intellectual disability	5 (15.2)	1 (0.8)
Risk factors in 2 months before index date (number [%])		
Major injury	-	-
Prolonged immobility	2 (6.1)	-
Surgery	-	-
Pregnancy	-	3 (2.3)
Smoking status (number [%])		
Non-smoker	8 (24.2)	35 (26.5)
Smoker	7 (21.2)	33 (25.0)
Ex-smoker	4 (12.1)	10 (7.6)
Status not recorded	14 (42.4)	54 (40.9)

Characteristic	Cases (n=33)	Controls (n=132)
Weight category (number [%])		
Low (< 60 kg)	2 (6.1)	32 (24.2)
Medium (60 – 70 kg)	6 (18.2)	33 (25.0)
High (> 70 kg)	14 (42.4)	30 (22.7)
Weight not measured	11 (33.3)*	37 (28.0)†
Prescribed medicines, excluding contraception and HRT		
In year before index date	26 (78.8)	98 (74.2)
In 3 months before index date		
Yes	18 (54.5)	56 (42.4)
Possible	1 (3.0)	12 (9.1)
Pregnancy history		
Ever pregnant	18 (54.5)	80 (60.6)
One or more live births	15 (45.5)	73 (55.3)
Menopausal status		
Natural menopause	-	2 (1.5)
Artificial menopause		
Hysterectomy only	-	5 (3.8)
Hysterectomy and bilateral oophorectomy	-	1 (0.8)
Cyclophosphamide (antineoplastic)	1 (3.0)	-
Peri-menopausal symptoms	1 (3.0)	5 (3.8)
Family history of venous thromboembolism	-	-

* Comments in the records of one of these cases indicated that she was overweight. She had a history of venous thromboembolism and hence was excluded from the key analyses.
† Comments in the records of one of these controls indicated that she was of average weight.

5.3.2 Ever and current use of contraceptive methods

Table 5.8 provides a summary of the various methods of contraception used by cases and controls before the index date. Twenty-five (78.1%) cases and 60 (48.4%) controls were current users of at least one method. Oral contraceptives were the most commonly used past and current method. Twenty-eight (84.8%) cases and 88 (66.7%) controls had taken the pill at some time before the index date. Among pre-menopausal women, 20 (62.5%) cases and 26 (21.0%) controls were current users. Seven (21.2%) cases and 40 (30.3%) controls had used the progestogen-only pill, although only 3% of the pre-menopausal women in each group were current users. Cases were less likely than controls to be current users of medroxyprogesterone acetate, intrauterine devices, and female sterilisation. There were similar proportions of pre-menopausal cases and controls in the three months before the index date whose partners had had a vasectomy.

Because these data refer to recorded contraceptive use, it is likely that the prevalence of condom use has been underestimated because condoms can be purchased without a prescription in New Zealand. It is also possible that the use of sterilisation, especially of male partners, has been underestimated. However, it is not expected that this would have differed between cases and controls. Information about the other contraceptive methods is more likely to be complete because they all require a prescription or a medical intervention.

Table 5.8 Ever and current use of contraceptive methods by female cases and controls aged 15 – 49 years

Method	Ever use (number [% of all women])		Current use (number [% of pre-menopausal])	
	Cases (n=33)	**Controls (n=132)**	**Cases (n=32)**	**Controls (n=124)**
Oral contraceptives	28 (84.8)	88 (66.7)	20 (62.5)	26 (21.0)
Progestogen-only pill	7 (21.2)	40 (30.3)	1 (3.1)	4 (3.2)
Medroxyprogesterone acetate	5 (15.2)	16 (12.1)	1 (3.1)	9 (7.3)
Morning after pill	3 (9.1)	16 (12.1)	-	-
Intrauterine device	4 (12.1)	15 (11.4)	-	3 (2.4)
Diaphragm	1 (3.0)	3 (2.3)	-	-
Condoms*	6 (18.2)	32 (24.2)	1 (3.1)	1 (0.8)
Female sterilisation†	1 (3.0)	14 (10.6)	1 (3.1)	10 (8.1)
Partner vasectomy‡	4 (12.1)	8 (6.1)	2 (6.3)	7 (5.6)
Natural family planning	2 (6.1)	2 (1.5)	-	-
Other	1 (3.0)	8 (6.1)	-	1 (0.8)

* The case and control who were current users of condoms were also using oral contraceptives.
† Four controls who had undergone female sterilisation were post-menopausal in the three months before the index date.
‡ The partner of one case had a reversal of his vasectomy, and in the three months before the index date one case and one control (whose previous partners had had vasectomies) had new partners who had not been sterilised.

5.3.3 Ever use of oral contraceptives

Table 5.9 shows the number of different oral contraceptive preparations ever used by cases and controls. Formulations that contained the same progestogen but different doses of the progestogen and / or oestrogen components were counted as different preparations. The majority of both cases (67.9%) and controls (71.6%) had been prescribed, at most, two different preparations before the index date. If preparations containing the same progestogen, but different doses of oestrogen and / or progestogen, were counted only once, 20 (71.4%) cases and 72 (81.8%) controls had been exposed to a maximum of two different progestogens.

Table 5.10 shows the numbers of cases and controls who had been prescribed the various types of progestogen at any time before the index date. Eighteen (64.3%) cases and 40 (45.5%) controls had been prescribed an oral contraceptive containing desogestrel. Gestodene was less commonly prescribed for both cases (25.0%) and controls (27.3%). Half of the controls had been prescribed levonorgestrel-containing oral contraceptives as compared with only a quarter of the cases. Cases were twice as likely to have used lynoestrenol and half as likely to have taken norethisterone as controls.

Table 5.9 Number of different oral contraceptive preparations ever used by cases and controls aged 15 – 49 years

Number of preparations prescribed	Progestogen contained in prescribed preparation*	Ever users (number [%])	
		Cases (n=28)	Controls (n=88)
One	Desogestrel	3	11
	Gestodene	3	4
	Levonorgestrel	2	8
	Cyproterone acetate	1	1
	Norethisterone	-	4
	Lynoestrenol	-	2
	Norgestrel	-	1
	Preparation not specified	2	2
	Total (% ever users)	**11 (39.3)**	**33 (37.5)**
Two	Desogestrel, desogestrel	1	1
	Desogestrel, gestodene	3	3
	Desogestrel, levonorgestrel	1	3
	Desogestrel, norethisterone	-	3
	Desogestrel, lynoestrenol	1	-
	Desogestrel, preparation not specified	2	2
	Gestodene, levonorgestrel	-	5
	Gestodene, preparation not specified	-	1
	Levonorgestrel, levonorgestrel	-	3
	Levonorgestrel, norethisterone	-	2
	Levonorgestrel, lynoestrenol	-	1
	Levonorgestrel, megestrol acetate	-	1
	Levonorgestrel, preparation not specified	-	4
	Norethisterone, norgestrel	-	1
	Total (% ever users)	**8 (28.6)**	**30 (34.1)**
Three	Desogestrel, desogestrel, gestodene	-	2
	Desogestrel, desogestrel, levonorgestrel	-	1
	Desogestrel, gestodene, levonorgestrel	-	1
	Desogestrel, gestodene, preparation not specified	1	-
	Desogestrel, levonorgestrel, levonorgestrel	-	1
	Desogestrel, levonorgestrel, preparation not specified	1	-
	Desogestrel, norethisterone, preparation not specified	-	1
	Desogestrel, levonorgestrel, lynoestrenol	1	-
	Desogestrel, lynoestrenol, lynoestrenol	1	-

Number of preparations prescribed	Progestogen contained in prescribed preparation*	Ever users (number [%])	
		Cases (n=28)	Controls (n=88)
Three (ctd)	Gestodene, levonorgestrel, levonorgestrel	-	1
	Gestodene, lynoestrenol, preparation not specified	-	1
	Levonorgestrel, levonorgestrel, norethisterone	-	1
	Levonorgestrel, levonorgestrel, norgestrel	-	1
	Levonorgestrel, lynoestrenol, preparation not specified	1	-
	Total (% ever users)	**5 (17.9)**	**10 (11.4)**
Four	Desogestrel, desogestrel, gestodene, levonorgestrel	-	2
	Desogestrel, desogestrel, levonorgestrel, norethisterone	-	1
	Desogestrel, levonorgestrel, levonorgestrel, levonorgestrel	-	1
	Desogestrel, levonorgestrel, levonorgestrel, norethisterone	-	2
	Desogestrel, levonorgestrel, norethisterone, ethynodiol diacetate	-	1
	Desogestrel, cyproterone acetate, norethisterone, lynoestrenol	1	-
	Gestodene, levonorgestrel, lynoestrenol, preparation not specified	-	1
	Levonorgestrel, levonorgestrel, levonorgestrel, ethynodiol diacetate	-	1
	Levonorgestrel, levonorgestrel, norethisterone, lynoestrenol	-	1
	Levonorgestrel, levonorgestrel, norethisterone, preparation not specified	1	-
	Total (% ever users)	**2 (7.1)**	**10 (11.4)**
Five	Desogestrel, desogestrel, gestodene, lynoestrenol, preparation not specified	-	1
	Desogestrel, levonorgestrel, levonorestrel, norethisterone, lynoestrenol	-	1
	Desogestrel, levonorgestrel, levonorgestrel, lynoestrenol, ethynodiol diacetate	1	-
	Total (% ever users)	**1 (3.6)**	**2 (2.3)**
Six	Desogestrel, desogestrel, gestodene, cyproterone acetate, levonorgestrel, lynoestrenol	-	1
	Levonorgestrel, levonorgestrel, norethisterone, lynoestrenol, norgestrel, megestrol	-	1
	Total (% ever users)	**-**	**2 (2.3)**
Seven	Desogestrel, desogestrel, gestodene, norethisterone, norethisterone, lynoestrenol, norgestrel	-	1
	Desogestrel, desogestrel, levonorgestrel, levonorgestrel, norethisterone, lynoestrenol, ethynodiol diacetate	1	-
	Total (% ever users)	**1 (3.6)**	**1 (1.1)**

* Progestogens are listed in order from the most to the least recently used.

Table 5.10 Progestogens contained in oral contraceptives ever used by cases and controls aged 15 – 49 years

Progestogen	**Cases (number [% ever users])***	**Controls (number [% ever users])†**
Desogestrel	18 (64.3)	40 (45.5)
Gestodene	7 (25.0)	24 (27.3)
Levonorgestrel	7 (25.0)	46 (52.3)
Cyproterone acetate	2 (7.1)	2 (2.3)
Norethisterone	3 (10.7)	20 (22.8)
Lynoestrenol	7 (25.0)	11 (12.5)
Norgestrel	-	5 (5.7)
Megestrel	-	2 (2.3)
Ethynodiol diacetate	2 (7.1)	2 (2.3)
Not specified	8 (28.6)	13 (14.8)

* 28 cases were ever users of oral contraceptives.
† 88 controls were ever users of oral contraceptives.

5.3.4 Current use of oral contraceptives

Details of the oral contraceptive preparations that were used by cases and controls during the three months before the index date are shown in Table 5.11. Seventy-five percent of the current pill use by cases was of oral contraceptives containing desogestrel or gestodene, as compared with 61.5% of the controls.

An additional case and three controls were classified as possible users of oral contraceptives in the three months before the index date. A 30 year old case, the woman who was confined to a wheelchair because of spina bifida, had been prescribed a desogestrel-containing oral contraceptive for a few years in the past. She had also used the morning after pill. Ten weeks before the index date her general practitioner noted that she required contraception, but did not record whether a prescription for any method had been provided.

Three weeks before the index date a gynaecologist, to whom a 20 year old control had been referred regarding pelvic pain, wrote to the patient's general practitioner and related a history of poor tolerance to oral contraceptives, of which she had tried several, including one containing desogestrel. This woman had only recently joined her general practice and there was no other documented history of oral contraceptive use.

Four months before index date the general practitioner of a 29 year old control noted that she was "on the pill". Seven months earlier she had been prescribed a six-month supply of a pill containing desogestrel — a preparation that she had taken, with a few breaks, over a period of six years.

Five months before the index date the general practitioner of a 23 year old control noted that she was "still taking" an oral contraceptive containing gestodene. The records indicated that she had been given a three-month supply of this preparation four months earlier when she had switched from a desogestrel-containing pill which she had taken since her early teens.

Tables 5.12 and 5.13 show the duration of the current episode of use for two groups of cases and controls: those for whom the current episode was the first ever documented episode and those who had taken the pill at some time in the past. As can be seen in

Table 5.12, there were only three cases and seven controls who were so-called "first-time users". Apart from one case who had been first prescribed the pill three months before the index date, and two controls who had received their first prescription a few days before the index date, all of the women had been users for at least 15 months. Among current users who had had previous episodes of oral contraceptive use, four (23.5%) of 17 cases and four (21.0%) of 19 controls had restarted the pill in the three months before the index date.

Table 5.11 Current and possible current use of oral contraceptive preparations by cases and controls aged 15 – 49 years by preparation

Preparation		Current use (number)		Possible current use (number)	
Progestogen	**Oestrogen**	**Cases**	**Controls**	**Cases**	**Controls**
Norethisterone 500µg	Ethinyloestradiol 35µg	-	1	-	-
Levonorgestrel 150µg	Ethinyloestradiol 30µg	2	4*	-	-
Levonorgestrel 125µg	Ethinyloestradiol 50µg	-	1	-	-
Levonorgestrel 250µg	Ethinyloestradiol 50µg	-	1	-	-
Levonorgestrel 50/75/125µg	Ethinyloestradiol 30/40/30µg	1	2	-	-
Desogestrel 150µg	Ethinyloestradiol 20µg	6	5†	-	1
Desogestrel 150µg	Ethinyloestradiol 30µg	4	5	-	-
Desogestrel 25/125µg	Ethinyloestradiol 40/30µg	-	1‡	-	-
Gestodene 75µg	Ethinyloestradiol 30µg	5	5	-	1
Cyproterone acetate 2000µg	Ethinyloestradiol 35µg	2§	1	-	-
Unknown	-	-	-	1	1
Total		**20**	**26**	**1**	**3**

* Two of these controls were matched with a case with a history of venous thromboembolism and are therefore excluded from the matched analyses.

† One of these controls conceived while apparently taking the pill and is therefore excluded from analyses from which women who were pregnant in the two months were excluded.

‡ During the three months before the index date, this woman switched from a preparation containing gestodene 75µg and ethinyloestradiol 30µg to the biphasic desogestrel-containing pill.

§ During the three months before the index date, one of these cases switched from a preparation containing desogestrel 150µg and ethinyloestradiol 30µg to the preparation containing cyproterone acetate.

Table 5.12 Current users of oral contraceptives for whom this was the first episode of use

Age (years)	Preparation	Duration of use
Cases (n=3)		
19.7	Gestodene 75µg / Ethinyloestradiol 30µg	3 months
22.8	Desogestrel 150µg / Ethinyloestradiol 20µg	18 months
26.7	Gestodene 75µg / Ethinyloestradiol 30µg	3 years
Controls (n=7)		
20.0	Gestodene 75µg / Ethinyloestradiol 30µg	21 months
20.3	Desogestrel 150µg / Ethinyloestradiol 30µg	15 months
26.4	Levonorgestrel 150µg / Ethinyloestradiol 30µg	3.6 months
28.8	Desogestrel 150µg / Ethinyloestradiol 30µg	2 days
29.2	Norethisterone 500µg / Ethinyloestradiol 35µg	5 years
29.9	Cyproterone acetate 2000µg / Ethinyloestradiol 35µg	32 months
36.7	Gestodene 75µg / Ethinyloestradiol 30µg	4 days

Table 5.13 Duration of current episode of use of oral contraceptives, women with previous episodes of use

Duration of current episode of use	Cases	Controls
< 1 month	2*	3†
1 – 2 months	2	1
3 – 5 months	2	2‡
6 – 8 months	3§	4
9 – 11 months	3	1
12 – 23 months	3	5
≥ 24 months	2‖	3¶
Total	**17**	**19**

* One case switched directly from another preparation to the one she was taking on the index date.
† One control switched directly from another preparation to the one she was taking on the index date.
‡ One control switched directly from another preparation to the one she was taking on the index date.
§ One case switched directly from another preparation to the one she was taking on the index date.
‖ One case switched directly from another preparation to the one she was taking on the index date.
¶ Two controls switched directly from another preparation to the one they were taking on the index date.

5.3.5 Estimated relative risk of fatal pulmonary embolism in current users of oral contraceptives

As was discussed in the previous chapter, a matched analysis produced unstable estimates of the risk of fatal pulmonary embolism in current users of oral contraceptives. Hence, unmatched analyses were undertaken, using unconditional logistic regression, and the matching factors (age and general practice) were accounted for in the analyses. Post-menopausal women and those with a history of venous thromboembolism were excluded from all analyses. In additional analyses, those who were pregnant or immobilised during the two months before the index date were also excluded. One case and five controls had reported peri-menopausal symptoms (such as hot flushes and changes in menstruation) before the index date. It was decided not to exclude these women (apart from one control who was excluded because her case had a history of venous thromboembolism), as low-dose oral contraceptives were sometimes prescribed for women with such symptoms during the study period. Similarly, the pre-menopausal control who was a current user of hormone replacement therapy, and the pre-menopausal case and controls who were past users, were not excluded.

Tables 5.14 – 5.16 show the key results. In the first of these analyses, shown in Table 5.14, only those women who were post-menopausal or had a history of venous thromboembolism were excluded. Non-users (never and past users combined) were the reference category. The matching factors (age and general practice) were accounted for by adjusting the odds ratios for age as a continuous variable and adjusting the standard errors for clustering by practice. As expected, if these factors were ignored, the odds ratios were biased towards the null value. Hence, the unadjusted odds ratio for current use of any oral contraceptive was 7.5 (95% CI 3.1 – 18.1), whereas the estimate adjusted for age and clustering by practice was 10.1 (95% CI 3.7 – 27.3). Adjusting for the weight category had little impact (odds ratio 10.7 [95% CI 3.8 – 30.2]). Current use of antipsychotic drugs did not confound the association.

When controls who were pregnant during the two months before the index date (which included one control who had also taken the pill during that period) were excluded (Table 5.15), the odds ratio (adjusted for age, weight category, and clustering by practice) did not change (10.7 [95% CI 3.7 – 30.5]). If the case who was confined to a wheelchair (who was a possible current user) was also excluded, the adjusted odds ratio

was 13.1 (95% CI 4.4 – 39.0) (Table 5.16). Excluding the controls of the excluded cases had minimal impact on the odds ratio, although the precision of the estimate was naturally decreased (odds ratio 13.8 [95% CI 4.6 – 41.4]).

When the possible users of oral contraceptives were recoded as current users, and four groups of women were excluded (those who were post-menopausal or had a history of venous thromboembolism, and those who were immobilised or pregnant in the two months before the index date), the odds ratio (adjusted for age, weight category, and clustered on practice) was 12.4 (95% CI 4.0 – 38.5).

In all analyses, current users of oral contraceptives containing levonorgestrel had about a five-fold increased risk of dying from pulmonary embolism when compared with non-users. As can be seen in Table 5.16, when women who were post-menopausal or had a history of venous thromboembolism and those who were immobilised or pregnant in the two months before the index date were excluded, the adjusted odds ratio was 5.9 (95% CI 1.4 – 25.6). Pills containing desogestrel or gestodene carried a higher risk; the adjusted odds ratio for these preparations was 18.8 (95% CI 4.9 – 71.3). The greatest risk was estimated for users of contraceptives containing cyproterone acetate; the adjusted odds ratio was 20.1 (95% CI 4.4 – 91.4).

An analysis was also undertaken in which current use was re-defined as prescribed use during the month before the index date (Table 5.17). This analysis, in which one case and four controls were re-classified as non-users, produced results that were consistent with those obtained for use during the three months before the index date. After excluding women who were post-menopausal or had a history of venous thromboembolism and those who were immobilised or pregnant in the two months before the index date, the odds ratio for use of any oral contraceptive was 10.7 (95% CI 3.7 – 30.6).

Table 5.14 Current use of oral contraceptives and fatal pulmonary embolism, excluding women who were post-menopausal or had a history of venous thromboembolism

Progestogen in oral contraceptive	Cases (n=30)	Controls (n=124)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	Adjusted odds ratio (95% CI)†
Non-user	10	98	1.0	1.0	1.0
Levonorgestrel	3	8	3.7 (0.8 – 16.3)	4.9 (1.3 – 18.9)	5.0 (1.2 – 21.4)
Desogestrel or gestodene	15	16	9.3 (3.6 – 24.2)	12.6 (3.7 – 42.4)	15.2 (4.3 – 53.3)
Cyproterone acetate	2	1	19.8 (1.6 – 238.1)	26.1 (6.4 – 105.9)	14.9 (3.2 – 68.8)
All types	20	26‡	7.5 (3.1 – 18.1)	10.1 (3.7 – 27.3)	10.7 (3.8 – 30.2)

* Adjusted for age as a continuous variable and clustered on general practice.
† Adjusted for age as a continuous variable, weight (four categories, including missing values), and clustered on general practice.
‡ One control was using an oral contraceptive containing norethisterone.

Table 5.15 Current use of oral contraceptives and fatal pulmonary embolism, excluding women who were post-menopausal or had a history of venous thromboembolism, and those who were pregnant in the two months before the index date

Progestogen in oral contraceptive	Cases (n=30)	Controls (n=121)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	Adjusted odds ratio (95% CI)†
Non-user	10	96	1.0	1.0	1.0
Levonorgestrel	3	8	3.6 (0.8 – 15.9)	4.8 (1.2 – 18.6)	4.9 (1.1 – 20.7)
Desogestrel or gestodene	15	15‡	9.7 (3.7 – 25.5)	13.2 (3.7 – 47.2)	15.5 (4.3 – 55.7)
Cyproterone acetate	2	1	19.4 (1.6 – 233.3)	25.7 (6.3 – 104.3)	14.6 (3.1 – 67.7)
All types	20	25§	7.7 (3.2 – 18.5)	10.3 (3.7 – 28.5)	10.7 (3.7 – 30.5)

* Adjusted for age as a continuous variable and clustered on general practice.
† Adjusted for age as a continuous variable, weight (four categories, including missing values), and clustered on general practice.
‡ One control who was taking a desogestrel-containing oral contraceptive was also pregnant during the two months before the index date and was therefore excluded from these analyses.
§ One control was using an oral contraceptive containing norethisterone.

Table 5.16 Current use of oral contraceptives and fatal pulmonary embolism, excluding women who were post-menopausal or had a history of venous thromboembolism, and those who were immobilised or pregnant in the two months before the index date

Progestogen in oral contraceptive	Cases (n=29)	Controls (n=121)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	Adjusted odds ratio (95% CI)†
Non-user	9	96	1.0	1.0	1.0
Levonorgestrel	3	8	4.0 (0.9 – 18.0)	5.7 (1.4 – 22.6)	5.9 (1.4 – 25.6)
Desogestrel or gestodene	15	15‡	10.8 (4.0 – 29.0)	15.8 (4.3 – 58.0)	18.8 (4.9 – 71.3)
Cyproterone acetate	2	1	21.6 (1.8 – 261.5)	30.5 (7.4 (125.0)	20.1 (4.4 – 91.4)
All types	20	25§	8.5 (3.5 – 21.0)	12.3 (4.3 – 35.0)	13.1 (4.4 – 39.0)

* Adjusted for age as a continuous variable and clustered on general practice.
† Adjusted for age as a continuous variable, weight (four categories, including missing values), and clustered on general practice.
‡ One control who was taking a desogestrel-containing oral contraceptive was also pregnant during the two months before the index date and was therefore excluded from these analyses.
§ One control was using an oral contraceptive containing norethisterone.

Table 5.17 Use of oral contraceptives in the month before the index date and fatal pulmonary embolism, excluding women who were post-menopausal or had a history of venous thromboembolism, and those who were immobilised or pregnant in the two months before the index date

Progestogen in oral contraceptive	Cases (n=29)	Controls (n=121)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	Adjusted odds ratio (95% CI) †
Non-user	10	99	1.0	1.0	1.0
Levonorgestrel	2	7	2.9 (0.5 – 15.6)	3.5 (0.7 – 17.3)	3.0 (0.7 – 13.8)
Desogestrel or gestodene	15	13‡	11.5 (4.3 – 31.0)	14.9 (4.3 – 51.9)	17.3 (4.6 – 64.6)
Cyproterone acetate	2	1	20.0 (1.7 – 240.5)	25.5 (6.2 – 104.7)	16.6 (3.7 – 74.7)
All types	19	22§	8.6 (3.5 – 20.9)	10.8 (3.9 – 29.7)	10.7 (3.7 – 30.6)

* Adjusted for age as a continuous variable and clustered on general practice.
† Adjusted for age as a continuous variable, weight (four categories, including missing values), and clustered on general practice.
‡ One control who was taking a desogestrel-containing oral contraceptive was also pregnant during the two months before the index date and was therefore excluded from these analyses.
§ One control was using an oral contraceptive containing norethisterone.

Absolute risk of fatal pulmonary embolism in current users of oral contraceptives

Contraceptive-supply data obtained from the Ministry of Health showed that there were up to 1, 717,153 woman-years of use of oral contraceptives between 1 January 1990 and 31 August 1998. During that period, 17 of the oral contraceptive users in the present study died from pulmonary embolism. A further death from pulmonary embolism (confirmed by necropsy) during the same period, of a woman taking an oral contraceptive containing desogestrel, was notified to the Centre for Adverse Reactions Monitoring. This death had been miscoded in national mortality data. Hence, the absolute risk of death from idiopathic pulmonary embolism in women taking oral contraceptives was estimated to be 10.5 (95% CI 6.2 – 16.6) per million woman-years. It is possible that this represents an underestimate of the true mortality, since it is not known whether any of the seven women aged 15 – 49 years for whom general practitioner records could not be located were current users of oral contraceptives.

5.3.6 Cases reported to the Centre for Adverse Reactions Monitoring

Only seven (35%) of the 20 deaths identified in the present study that occurred between 1 January and 31 December 1998 among women using oral contraceptives had been reported to the Centre for Adverse Reactions Monitoring.

5.4 HORMONE REPLACEMENT THERAPY

5.4.1 Introduction

Findings regarding hormone replacement therapy will be presented briefly, even though it was recognised that the study would have insufficient power to look at this issue. In previous surveys of hormone replacement therapy among New Zealand women during the study period, the highest proportions of current users were found among women aged 50 – 54 years and 55 – 59 years (North and Sharples 2001). For this reason, analyses exploring the association between hormone replacement therapy and fatal pulmonary embolism were confined to women aged 50 – 59 years.

5.4.2 Characteristics of female cases and controls aged 50 – 59 years

Eighteen female cases were aged between 50 and 59 years on the index date; the median age of these cases (and their controls) was 56.0 years. Four cases and two controls had

a history of venous thromboembolism. One of the two controls had also had surgery in the two months before the index date and, in addition, was matched to a case with a history of venous thromboembolism. A third control had surgery in the two months before the index date. These women were all excluded from the key analyses. Two controls who had a history of breast cancer were also excluded because the prescription of hormone replacement therapy was generally contraindicated for women with such malignancies.

A documented history of condom use during the three months before the index date was found for one case and four controls. No other women were recorded as using contraception during that period. Sixteen (88.9%) cases and 48 (66.7%) controls were current users of medicines other than hormone replacement therapy during the three months before the index date.

5.4.3 Ever use of hormone replacement therapy

Ten (55.6%) cases and 40 (55.6%) controls had ever used hormone replacement therapy before the index date. Table 5.18 shows the various regimens that were used by these women. Oestrogen-only regimens were the most commonly prescribed, and had been used at some time before the index date by eight (44.4%) cases and 26 (36.1%) controls. Six cases and 15 controls had a recorded history of hysterectomy; none of these women had taken hormone replacement before their surgery (Table 5.19). Of the four cases and 25 controls with no recorded history of hysterectomy, two cases and 13 controls had used oestrogen-only preparations at some time before the index date.

Table 5.18 Ever use of hormone replacement therapy by female cases and controls aged 50 – 59 years

Regimens used	**Ever use (number [%])**	
	Cases (n=18)	**Controls (n=72)**
Oestrogen-only	6 (33.3)	17 (23.6)
Sequential combined oestrogen / progestogen	2 (11.1)	9 (12.5)
Continuous combined oestrogen / progestogen	-	3 (4.2)
Oestrogen-only and sequential combined oestrogen / progestogen	2 (11.1)	5 (6.9)
Oestrogen-only, sequential, and continuous combined oestrogen / progestogen	-	2 (2.8)
Oestrogen-only and continuous combined oestrogen / progestogen	-	2 (2.8)
Sequential combined and continuous combined oestrogen / progestogen	-	1 (1.4)
Sequential combined oestrogen / progestogen and testosterone	-	1 (1.4)
Total (%)	**10 (55.6)**	**40 (55.6)**

Table 5.19 Hormone replacement therapy regimens ever used by history of hysterectomy

Regimens ever used	Cases (n=18)		Controls (n=72)	
	No record of hysterectomy	**Post-hysterectomy***	**No record of hysterectomy**	**Post-hysterectomy***
Oestrogen-only	2	4	7	10
Combined oestrogen / progestogen†	2	-	12	2‡
Oestrogen-only and combined oestrogen / progestogen	-	2	6	3
Total	**4**	**6**	**25**	**15**

* No cases or controls used hormone replacement therapy before undergoing a hysterectomy.
† Sequential or continuous combined regimens.
‡ One control took a sequential combined regimen along with testosterone.

5.4.4 Current use of hormone replacement therapy

Six cases and 15 controls were current users of hormone replacement therapy (Table 5.20). Two of these women (one case and one control) had a history of deep vein thrombosis. The control had also undergone surgery in the two months before the index date. There were no possible users of hormone replacement therapy in the three months before the index date.

Table 5.20 Current use of hormone replacement therapy

Regimen		Current use	
Oestrogen	**Progestogen**	**Cases (n=18)**	**Controls (n=72)**
Oestrogen-only			
Conjugated equine oestrogen 0.3mg	-	-	1
Conjugated equine oestrogen 0.625mg	-	3*	3†
Conjugated equine oestrogen 1.25mg	-	1	1
Oestradiol, dose not specified	-	-	1
Oestradiol TTS 100µg	-	-	1
Sequential combined			
Conjugated equine oestrogen 0.625mg	Medroxyprogesterone acetate 10mg	-	1
Conjugated equine oestrogen 0.625mg	Norgestrel 0.15mg	-	1
Conjugated equine oestrogen 1.25mg	Norgestrel 0.3mg	1‡	-
Ethinyloestradiol 0.01mg	Medroxyprogesterone acetate 5mg	1	-
Oestradiol TTS 25µg	Medroxyprogesterone acetate 5mg	-	1
Oestradiol TTS 50µg	Medroxyprogesterone acetate 5mg	-	1§
Oestradiol TTS 50µg	Norethisterone acetate 1mg	-	1
Oestradiol valerate 3mg	Norgestrel 0.5mg	-	1
Continuous combined			
Conjugated equine oestrogen 0.625mg	Medroxyprogesterone acetate 2.5mg	-	1
Oestradiol 2mg	Norethisterone acetate 1mg	-	1
Total		**6**	**15**

* One case had a history of venous thromboembolism. During the three months before the index date, the doctor of this case changed her regimen from 0.3mg of conjugated equine oestrogen to 0.625mg.
† One control had a history of venous thromboembolism (as did her case) and of surgery in the two months before the index date.
‡ During the three months before the index date, the doctor of this case changed her regimen from conjugated equine oestrogen 0.625mg plus norgestrel 0.15mg to conjugated equine oestrogen 1.25mg plus norgestrel 0.3mg.
§ During the three months before the index date, the doctor of this case changed her regimen from oestradiol TTS 25µg plus medroxyprogesterone 5mg to oestradiol TTS 50µg plus medroxyprogesterone 5mg.

5.4.5 Estimated relative risk of fatal pulmonary embolism in current users of hormone replacement therapy

The results of matched and unmatched analyses are shown in Tables 5.21 and 5.22 respectively. Women with a history of venous thromboembolism, breast cancer, or surgery in the two months before the index date were excluded and non-users were taken as the reference category. In the matched analysis, based on 14 cases and 52 controls, current use of hormone replacement therapy was associated with a non-significant three-fold increased risk of dying from pulmonary embolism. The unmatched analysis, which was based on 14 cases and 67 controls, produced similar results; the odds ratio (adjusted for age, weight category, current use of antipsychotic drugs, and clustered on general practice) was 3.0 and was of borderline significance (95% CI 1.0 – 8.4).

Table 5.21 Current use of hormone replacement therapy and fatal pulmonary embolism, matched analysis*

HRT	Cases (n=14)	Controls (n=52)	Unadjusted matched odds ratio (95% CI)	Adjusted matched odds ratio (95% CI)†	Adjusted matched odds ratio (95% CI)‡
Non-user	9	41	1.0	1.0	1.0
User§	5	11	2.3 (0.6 – 9.3)	2.9 (0.5 – 18.0)	3.3 (0.5 – 21.7)

* Excluding all women who had a history of venous thromboembolism, breast cancer, or surgery in the two months before the index date. No women had a major injury or prolonged immobility in the two months before the index date.
† Adjusted for weight (four categories, including missing values).
‡ Adjusted for weight (four categories, including missing values) and use of antipsychotic drugs in the three months before index date.
§ All regimens combined.

Abbreviation used in the table HRT: hormone replacement therapy.

Table 5.22 Current use of hormone replacement therapy and fatal pulmonary embolism, unmatched analysis*

HRT	Cases (n=14)	Controls (n=67)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)†	Adjusted odds ratio (95% CI)‡	Adjusted odds ratio (95% CI)§
Non-user	9	53	1.0	1.0	1.0	1.0
User‖	5	14	2.1 (0.6 – 7.3)	2.1 (0.6 – 6.9)	2.8 (1.0 – 8.2)	3.0 (1.0 – 8.4)

* Excluding all women who had a history of venous thromboembolism, breast cancer, or surgery in the two months before the index date. No women had a major injury or prolonged immobility in the two months before the index date.
† Adjusted for age as a continuous variable and clustered on general practice.
‡ Adjusted for age as a continuous variable, weight (four categories, including missing values), and clustered on general practice.
§ Adjusted for age as a continuous variable, weight (four categories, including missing values), use of antipsychotic drugs in the three months before index date, and clustered on general practice.
‖ All regimens combined.

Abbreviation used in the table HRT: hormone replacement therapy.

5.5 PSYCHOTROPIC DRUGS

5.5.1 Cases and controls included in the key analyses

The characteristics of the 75 cases and 300 controls who were considered for inclusion in the analyses which explored the association between psychotropic drugs and fatal pulmonary embolism were discussed in section 5.2. As shown in Table 5.5, 10 cases and two controls had a history of venous thromboembolism. During the two months before the index date, an additional three cases had a severe injury or prolonged immobility, a third control had major surgery and three controls were pregnant. These cases and controls were considered to have had major risk factors for venous thromboembolism and were therefore excluded from the main analyses. Because matched analyses were undertaken, the controls of excluded cases were also excluded. Hence, the key analyses were based on 62 cases (19 male, 43 female) and 243 controls (76 male, 167 female). The median ages of these cases and controls were 43.5 and 44.0 years respectively; the median ages of the female and male cases were 42.0 and 47.0 years respectively. The discussion in the following sections focuses on these 62 cases and 243 controls, although the tables also include results for all subjects.

5.5.2 Ever and current use of psychotropic drugs

Twenty-two (35.5%) cases and 39 (16.0%) controls had a history of being prescribed at least one psychotropic medicine at some time before the index date (Table 5.23). Three of the cases and seven of the controls were prescribed these drugs to treat non-psychiatric conditions such as epilepsy, shingles, insomnia, myoclonus, migraine prophylaxis, nausea associated with inner ear disease, and behavioural problems associated with an intellectual disability. The remaining 19 (30.6%) cases and 32 (13.2%) controls were treated for various mental illnesses, including depression, anxiety disorders, schizophrenia, and bipolar affective disorder.

Sixteen (25.8%) cases and 15 (6.2%) controls were current users of at least one psychotropic drug, of whom seven cases (43.8%) and four controls (26.7%) were current users of more than one type of psychotropic medicine (Table 5.25).

Table 5.23 Ever and current use of psychotropic drugs by cases and controls aged 15 – 59 years

Type of psychotropic drug	Ever use (number [%])		Current use (number [%])	
	Cases	**Controls**	**Cases**	**Controls**
All subjects (75 cases, 300 controls)				
Antipsychotic	13 (17.3)	8 (2.7)	9 (12.0)	3 (1.0)
Antidepressant	20 (26.7)	36 (12.0)	12 (16.0)	9 (3.0)
Other*	16 (21.3)	26 (8.7)	6 (8.0)	12 (4.0)
Any psychotropic drug†	**29 (38.7)**	**48 (16.0)**	**20 (26.7)**	**18 (6.0)**
Subjects without major risk factors (62 cases, 243 controls)‡				
Antipsychotic	11 (17.7)	5 (2.1)	8 (12.9)	2 (0.8)
Antidepressant	16 (25.8)	31 (12.8)	10 (16.1)	9 (3.7)
Other*	14 (22.6)	19 (7.8)	5 (8.1)	9 (3.7)
Any psychotropic drug§	**22 (35.5)**	**39 (16.0)**	**16 (25.8)**	**15 (6.2)**

* This group includes benzodiazepines, zopiclone, lithium carbonate, meprobamate, sodium valproate, and carbamazepine.
† Seven cases and five controls had used more than one type of psychotropic drug.
‡ No history of venous thromboembolism, or of prolonged immobility, severe injury, major surgery, or pregnancy during the two months before the index date.
§ Seven cases and four controls had used more than one type of psychotropic drug.

Table 5.24 Current use of psychotropic drugs

Current use of psychotropic drugs	Cases	Controls
All subjects (75 cases, 300 controls)		
Antipsychotic alone	3	1
Antidepressant alone	7	5
Other alone	3	7
Antipsychotic and antidepressant	4	-
Antipsychotic and other	2	1
Antipsychotic, antidepressant, and other	-	1
Antidepressant and other	1	3
Total	**20**	**18**
Subjects without major risk factors (62 cases, 243 controls)*		
Antipsychotic alone	2	1
Antidepressant alone	5	5
Other alone	2	5
Antipsychotic and antidepressant	4	-
Antipsychotic and other	2	-
Antipsychotic, antidepressant, and other	-	1
Antidepressant and other	1	3
Total	**16**	**15**

* No history of venous thromboembolism, or of prolonged immobility, severe injury, major surgery, or pregnancy during the two months before the index date.

Antipsychotic drugs

Use of antipsychotic drugs

Eight cases and two controls were current users of antipsychotic drugs. The median age of the cases who died while taking an antipsychotic drug was 47.0 years. Thioridazine, a low potency antipsychotic, was used by six cases and one control (Table 5.25). High potency antipsychotics were used by two cases (haloperidol) and by one control (prochlorperazine). There were no users of atypical agents.

All users, except for the control who was prescribed prochlorperazine for labyrinthitis six weeks before the index date, had received antipsychotic medication either continuously or intermittently over many years. Four cases and one control had a diagnosis of schizophrenia noted in their records, while another case had a possible diagnosis of schizophrenia recorded. Of the remaining cases, one had a bipolar affective disorder, one had an intellectual disability and was prescribed thioridazine for behavioural control, and one was taking thioridazine to treat insomnia. No user had an acute psychotic episode in the three months before the index date; one man was admitted to hospital following an overdose.

Table 5.25 Current use of antipsychotic drugs by cases and controls

Current use of antipsychotic drugs	Cases	Controls
All subjects (75 cases, 300 controls)		
Haloperidol	2	-
Thioridazine	7	1
Pimozide	-	1
Prochlorperazine	-	1
Total	**9**	**3**
Subjects without major risk factors (62 cases, 243 controls)*		
Haloperidol	2	-
Thioridazine	6	1
Prochlorperazine	-	1
Total	**8**	**2**

*No history of venous thromboembolism, or of prolonged immobility, severe injury, major surgery, or pregnancy during the two months before the index date.

Risk of fatal pulmonary embolism in current users of antipsychotic drugs

Tables 5.26 and 5.27 show the results of the matched analyses in which the risk of dying from pulmonary embolism was estimated for current users of antipsychotic drugs. Taking non-users (never and past users combined) as the reference group, the odds ratio (adjusted for weight category, oral contraceptive use, and hormone replacement therapy) for current use of any antipsychotic drug was 13.3 (95% CI 2.3 – 76.3). Low potency antipsychotics carried the highest risk, with an adjusted odds ratio of 20.8 (95% CI 1.7 – 259.0). Adding intellectual disability to the model had minimal impact to the estimate for use of any antipsychotic (odds ratio 12.8 [95% CI 2.1 – 77.9]).

The increased risk of pulmonary embolism in users of any antipsychotic persisted when women who were current users of oral contraceptives or hormone replacement therapy were excluded from the analysis, with an odds ratio (adjusted for weight category) of 8.3 (95% CI 1.3 – 53.5). Past use of antipsychotics, compared with never use, was not associated with a significantly elevated risk of pulmonary embolism (adjusted odds ratio 5.3 [95% CI 0.6 – 45.8]). The adjusted odds ratio for use of antipsychotic medication within one month of the index date was 11.2 (95% CI 1.9 – 65.4). An unmatched analysis (adjusted for age, sex, weight category, oral contraceptive use, hormone replacement therapy, and clustered on general practice) gave similar results to the matched analysis, with an odds ratio for antipsychotic use within three months of the index date of 14.1 (95% CI 3.3 – 61.1).

Table 5.26 Current use of any antipsychotic drug and fatal pulmonary embolism

Current use of any antipsychotic	Cases	Controls	Unadjusted matched odds ratio (95% CI)	Adjusted matched odds ratio (95% CI)*
All subjects (75 cases, 300 controls)				
Non-user	66	297	1.0	1.0
User	9	3	12.0 (3.2 – 44.3)	9.7 (2.3 – 40.9)
Subjects without major risk factors (62 cases, 243 controls)†				
Non-user	54	241	1.0	1.0
User	8	2	16.0 (3.4 – 75.3)	13.3 (2.3 – 76.3)

* Adjusted for weight (four categories, including missing values, for both sexes), oral contraceptive use, and hormone replacement therapy in the three months before the index date.
† No history of venous thromboembolism, or of prolonged immobility, severe injury, major surgery, or pregnancy during the two months before the index date.

Table 5.27 Current use of low potency antipsychotic drugs and fatal pulmonary embolism

Current use of low potency antipsychotic	Cases	Controls	Unadjusted matched odds ratio (95% CI)	Adjusted matched odds ratio (95% CI)*
All subjects (75 cases, 300 controls)†				
Non-user	66	297	1.0	1.0
User	7	1	28.0 (3.4 – 227.6)	29.3 (2.8 – 308.2)
Subjects without major risk factors (62 cases, 243 controls)‡				
Non-user	54	241	1.0	1.0
User	6	1	24.0 (2.9 – 199.3)	20.8 (1.7 – 259.0)

* Adjusted for weight (four categories, including missing values, for both sexes), oral contraceptive use, and hormone replacement therapy in the three months before the index date.
† Two cases and two controls were users of high potency antipsychotics, odds ratios not shown.
‡ No history of venous thromboembolism, or of prolonged immobility, severe injury, major surgery, or pregnancy during the two months before the index date. Two cases and one control without major risk factors were users of high potency antipsychotics, odds ratios not shown.

5.5.4 Antidepressant drugs

Use of antidepressant drugs

Four cases and one control used both antipsychotic and antidepressant drugs in the three months before the index date. When current users of antipsychotics (and their controls) were excluded, six cases and seven controls without major risk factors for venous thromboembolism were current users of antidepressants (Table 5.28). The median age of the cases was 53.3 years.

Tricyclic antidepressants were used by four cases and five controls. One of the four cases and a fifth were taking a selective serotonin reuptake inhibitor; the sixth case was taking a monoamine oxidase inhibitor. Of the remaining controls, one was using a selective serotonin reuptake inhibitor, while the other was taking a monoamine oxidase inhibitor.

None of the users had been admitted to hospital for depression during the three months before the index date, although two cases were diagnosed with acute depression and were prescribed tricyclics as outpatients about two months before the index date. Only one user, a control, was taking a tricyclic for a reason other than depression (migraine prophylaxis). Of the remaining users, one case first commenced treatment nine months before the index date, while all the others had been taking antidepressants intermittently or continuously for years.

Table 5.28 Current use of antidepressant drugs by cases and controls

Current use of antidepressants	Cases	Controls
All subjects (75 cases, 300 controls)		
Tricyclics		
Amitriptyline	2	2
Desipramine	1	-
Dothiepin	2	3
Nortriptyline	1	-
Trimipramine	2	2
Tetracyclics		
Maprotiline	1	-
Selective serotonin reuptake inhibitors		
Fluoxetine	2	2
Paroxetine	1	-
Monoamine oxidase inhibitors		
Isocarboxazid	-	1
Moclobemide	1	-
Total	**12***	**9†**
Subjects without major risk factors, current users of antipsychotics excluded (54 cases, 209 controls)‡		
Tricyclics		
Amitriptyline	1	2
Desipramine	1	-
Dothiepin	1	2
Trimipramine	1	1
Selective serotonin reuptake inhibitors		
Fluoxetine	2	1
Monoamine Oxidase Inhibitors		
Isocarboxazid	-	1
Moclobemide	1	-
Total	**6***	**7**

* One case was taking desipramine and fluoxetine.
† One control was taking dothiepin and fluoxetine.
‡ No history of venous thromboembolism, or of prolonged immobility, severe injury, major surgery, or pregnancy during the two months before the index date.

Risk of fatal pulmonary embolism in current users of antidepressant drugs

The results of the matched analysis are shown in Table 5.29. Taking non-users as the reference group, and excluding current users of antipsychotics, the odds ratio (adjusted for weight category, oral contraceptive use, and hormone replacement therapy) for current use of antidepressants was 4.9 (95% CI 1.1 – 22.5). The adjusted odds ratios for current and past use of antidepressants, compared to never use, were 6.3 (95% CI 1.3 – 30.8) and 2.9 (95% CI 0.7 – 11.5) respectively.

An analysis including current users of antipsychotics, but adjusting for such use, also found a five-fold increased risk in current users of antidepressants (odds ratio 5.5 [95% CI 1.3 – 23.8]). To explore the possibility that the risk of fatal pulmonary embolism in current users of antidepressants was modified by the use of antipsychotics (and vice versa) an interaction term was included in a conditional logistic regression model that included the following variables: weight category, and current use of antidepressants, antipsychotics, oral contraceptives, and of hormone replacement therapy. No evidence of an interaction was found.

Table 5.29 Current use of any antidepressant drug and fatal pulmonary embolism, excluding current users of antipsychotic drugs

Current use of any antidepressant	Cases	Controls	Unadjusted matched odds ratio (95% CI)	Adjusted matched odds ratio (95% CI) *
All subjects (66 cases, 261 controls)				
Non-user	58	254	1.0	1.0
User	8	7	5.5 (1.8 – 17.1)	10.0 (2.4 – 41.2)
Subjects without major risk factors (54 cases, 209 controls)†				
Non-user	48	202	1.0	1.0
User	6	7	3.7 (1.1 – 12.5)	4.9 (1.1 – 22.5)

* Adjusted for weight (four categories, including missing values, for both sexes), oral contraceptive use, and hormone replacement therapy in the three months before the index date.
† No history of venous thromboembolism, or of prolonged immobility, severe injury, major surgery, or pregnancy during the two months before the index date.

5.5.5 Other psychotropic drugs

Use of other psychotropic drugs

The prescribed use of other psychotropic drugs in the three months before the index date is shown in Table 5.30. Five cases and nine controls were current users of at least one psychotropic drug other than an antipsychotic or antidepressant.

Risk of fatal pulmonary embolism in current users of other psychotropic drugs

There appeared to be no increased risk for current or past use of other psychotropic drugs as a group. When users of antipsychotics or antidepressants were excluded, the adjusted odds ratio (adjusted for weight category, oral contraceptive use, and hormone replacement therapy during the three months before the index date) for current use was 1.4 (95% CI 0.3 – 7.7). Adjusting for antipsychotic and antidepressant use produced an identical point estimate (odds ratio 1.4 [95% CI 0.3 – 5.8]).

Table 5.30 Current use of other psychotropic drugs by cases and controls

Current use of other psychotropic drugs	Cases	Controls
All subjects (75 cases, 300 controls)		
Benzodiazepines	3	8
Lithium carbonate	2	1
Zopiclone	1	2
Carbamazepine	1	1
Sodium valproate	1	2
Meprobamate	-	1
Total	**5**[*]	**13**[†]
Subjects without major risk factors (62 cases, 243 controls)[‡]		
Benzodiazepines	3	6
Lithium carbonate	2	1
Zopiclone	1	1
Carbamazepine	1	1
Sodium valproate	1	1
Meprobamate	-	1
Total	**5**[§]	**9**[‖]

[*] One case was prescribed clonazepam, lithium carbonate, and zopiclone. Another was prescribed lithium carbonate and sodium valproate.
[†] One control was prescribed lithium carbonate and zopiclone. Another was prescribed carbamazepine and sodium valproate.
[‡] No history of venous thromboembolism, or of prolonged immobility, severe injury, major surgery, or pregnancy during the two months before the index date.
[§] One case was prescribed clonazepam, lithium carbonate, and zopiclone. Another was prescribed lithium carbonate and sodium valproate.
[‖] One control was prescribed lithium carbonate and zopiclone. Another was prescribed carbamazepine and sodium valproate.

CHAPTER 6 CASE-CONTROL STUDY OF THE USE OF ORAL CONTRACEPTIVES AND PSYCHOTROPIC DRUGS: DISCUSSION

6.1 SUMMARY OF MAIN FINDINGS

Because fatal pulmonary embolism is a rare condition, there were only 92 deaths between 1 January 1990 and 31 December 1998 among people aged 15 – 59 years, who were normally resident in New Zealand, in which pulmonary embolism was considered the underlying cause. Of these, the general practitioners of two men were not identified and the general practice records of a further 15 people were lost. Of the remaining 75 cases, 13 had major risk factors for venous thromboembolism. Hence, the key analyses which explored the association between psychotropic drugs and death from pulmonary embolism were based on 62 cases. Analyses which examined the risk in women using oral contraceptives were inevitably based on smaller numbers. This limited the precision of the estimates of relative risk, as demonstrated by the wide 95% confidence intervals. Nevertheless, when compared with non-use, prescribed use of any oral contraceptive in the three months before the index date was associated with a significant 10-fold increased risk of fatal pulmonary embolism. The odds ratio for use of contraceptives containing the so-called third generation progestogens, desogestrel and gestodene, was about three times higher than the point estimate for levonorgestrel contraceptives. Oral contraceptives containing cyproterone acetate appeared to carry the highest risk. Compared with non-users, current users of antipsychotic drugs had a 13-fold increased risk of fatal pulmonary embolism (odds ratio 13.3 [95% CI 2.3 – 76.3]).

Low potency antipsychotics carried a 20-fold increase in risk (odds ratio 20.8 [95% CI 1.7 – 259.0]), with thioridazine being the main drug involved. Antidepressant use in the three months before the index date was also associated with a significantly increased risk (odds ratio 4.9 [95% CI 1.1 – 22.5]). Because of the limited number of cases, it was not possible to examine the association between fatal pulmonary embolism and classes of psychotropic drugs other than antipsychotics and antidepressants.

6.2 POTENTIAL SOURCES OF BIAS TO BE CONSIDERED

Because case-control studies are particularly vulnerable to selection and information biases (Hennekens and Buring 1987), it is important to consider the potential role that bias may have played in the present study. The following discussion examines the possible sources of bias and considers whether they are a likely explanation for the observed associations between fatal pulmonary embolism and the use of oral contraceptives, antipsychotics, and antidepressants.

6.2.1 Ascertainment of cases

Because this was a population-based study, it was possible to include all deaths that occurred in New Zealand during the study period for which pulmonary embolism was considered the underlying cause. In almost all cases, the diagnosis of pulmonary embolism was confirmed by necropsy or other objective investigations. It is unlikely that any relevant deaths were missed because legal requirements to identify the cause of death (New Zealand Health Information Service 2001) mean that almost all people aged 15 – 59 years who die unexpectedly in New Zealand are referred for necropsy, generally at the request of a coroner. It is possible that deaths from pulmonary embolism in people with major health conditions (in whom death was not unexpected) might have gone unrecognised if a necropsy was not undertaken. However, even if detected, pulmonary embolism in these people should not, according to coding conventions, have been identified as the underlying cause of death and hence such people would not have been eligible for inclusion in the present study.

The general practice records of 75 (82%) of the 92 eligible cases were examined. The exclusion of the 15 cases for whom records were not available might have introduced some bias if the loss of the files was somehow related to the use of medicines and the underlying risk of venous thromboembolism. However, as was shown in Table 2.5, the absence of records was often because of practice-related reasons (such as doctors moving premises, retiring, or dying) and it did not appear to be related to particular characteristics of cases. This was especially reassuring in relation to the oral contraceptive analyses because there were threats of legal action during the period of data collection against general practitioners who had prescribed desogestrel and gestodene contraceptives (MacKinven 1999) and it was initially feared that this could adversely affect participation in the study. It is possible that the assurance that no

information about any named patient or doctor would be provided to any other party (Appendix A, letter 15) may have helped to maximise participation.

6.2.2 Selection of controls

Controls were randomly selected from the same general practices as the cases and were required to have been normally resident in New Zealand, and to have been members of those same practices, on the index date. Hence, the controls were drawn from the populations that gave rise to the cases. Although it is probable that some potential controls were not included in the sampling frame (because five general practices did not have an electronic age-sex register when the practice was visited and a further 16 practices had a register when visited but did not have one on the index date), the numbers involved are likely to have been small and hence this is unlikely to have created a substantial selection bias. Similarly, the refusal of two doctors in two group practices to allow their patients to be involved in the selection process is not expected to have had a meaningful impact.

The general practice records of 55 patients who were selected as potential controls had either been lost or transferred to another practice. Even if all of these patients had been members of the practice on the index date and hence eligible for inclusion (which is unlikely), the proportion of eligible controls who were included in the study would still have been high (85%).

In any event, there were no significant differences in the mean time that cases and controls had been members of their practices, or in the mean number of years of recorded medical information. Moreover, the frequency and type of contraceptives ever used, the prevalence of current use of oral contraceptives and hormone replacement therapy, and the life-time prevalence of treated mental illness observed among the controls was consistent with New Zealand population data from other sources (Pool et al. 1999; North and Sharples 2001; Oakley Browne et al. 2006), suggesting that the controls were indeed representative of the population from which the cases arose.

6.2.3 Information bias

Information about prescribed medicines and the medical history of cases and controls was derived from medical records, and hence was not subject to recall bias. It should be

recognised, however, that the absence of a recorded history of a particular condition or the use of a specific medicine did not necessarily mean that a case or control had never experienced such an event or used that medicine. This is because many patients did not attend the same general practice throughout their lives and, before the advent of electronic records, copies of medical files were not always transferred when a patient shifted to a new practice. However there was no evidence of a systematic difference between cases and controls in this regard — the mean number of years of recorded information was similar for both groups. Hence, the impact of any misclassification of risk factor status (that is, incorrectly classifying a person as having no history of a particular condition or event) is likely, if anything, have been to underestimate the effect size associated with that risk factor. In relation to medicine use, such a phenomenon is unlikely to have influenced the estimates of relative risk for current use since the date of the first recorded information was more than three months before the index date for all but two cases and four controls.

Clearly a history of being prescribed a medicine does not mean that patients actually delivered their prescription to a pharmacy or, indeed, that they took the medicine which was dispensed to them. Hence, it is possible that some cases and controls were classified as current users of a medicine when in fact they did not take the medicine. However, there was no reason to believe that cases and controls would have differed in such behaviours. Moreover it seems unlikely that there would be an association between poor adherence and an increased risk of venous thromboembolism since, unlike arterial thrombosis, there are no behavioural factors other than obesity that particularly modify the risk. Hence, any such misclassification of exposure status would have tended to lead to an underestimation of any association between current use of the medicine and fatal pulmonary embolism and thus cannot explain the increased risks observed in users of oral contraceptives, antipsychotics, and antidepressants.

The date of onset of the fatal episode (rather than the date of death) was taken as the index date, which is important for two reasons. First, it means that the prescription of antipsychotic or antidepressant drugs for unrecognised early symptoms of venous thromboembolism is an unlikely explanation for the increased risk of fatal pulmonary embolism observed in current users of these drugs. In any event, most of the cases had been taking their medicines for at least a year. Second, it means that it is unlikely that

the risks associated with the use of oral contraceptives and hormone replacement therapy were underestimated due to the cessation of the use of these medicines by women who had symptoms suggestive of venous thromboembolism.

Another source of bias to be considered is the possibility of error in the management of the data. The abstraction of information from medical records was all undertaken by me, and a systematic approach was employed to examine the medical files. Moreover, I had previously worked as a general practitioner, and as a medical officer in family planning clinics, and was familiar with how such records were compiled and the abbreviations commonly used. If it was not possible to decipher handwriting or abbreviations, assistance was sought from the relevant doctor. All data were coded and entered into an electronic spreadsheet by a research assistant and me. This double coding and data entry ensured that any errors could be identified and corrected.

6.3 POTENTIAL CONFOUNDING

Confounding by sex, age, weight, concomitant drug use, or underlying medical conditions is an unlikely explanation for the results obtained in the present study. People with advanced cancer, recent surgery, or pregnancy were excluded, and the key analyses were confined to people without a history of venous thromboembolism, recent injury, or prolonged immobility. Moreover, age and sex were accounted for in the analyses, and the risk estimates were adjusted for weight. It was not possible to adjust for BMI because the height of many patients was unrecorded. In the oral contraceptive analyses, adjustment for weight actually increased the estimated relative risks for the use of desogestrel and gestodene oral contraceptives and had little impact on the estimates for oral contraceptive use overall or for the use of levonorgestrel pills. Hence, if anything, residual confounding arising from adjusting for weight rather than BMI is likely to have produced conservative estimates. Adding weight alone to the multivariate models for antipsychotic and antidepressant use had minimal impact on the estimates of relative risk. The odds ratios for current use of psychotropic drugs were also adjusted for other relevant medicine use. The capacity to adjust for other potential confounders was inevitably limited by the small numbers, especially in the oral contraceptive analyses. However, the odds ratios for the use of oral contraceptives, antipsychotics,

and antidepressants all remained elevated in sensitivity analyses in which the estimates were additionally adjusted for a history of superficial venous thrombosis, varicose veins, intellectual disability, and a chronic musculoskeletal condition of the lower limbs.

6.4 ISSUES SPECIFIC TO ORAL CONTRACEPTIVES AND VENOUS THROMBOEMBOLISM

6.4.1 Consistency with other studies

Estimates of relative risk

The finding of a significantly increased risk of fatal pulmonary embolism in current users of oral contraceptives, when compared with non-users, is consistent with the results of the first (Inman and Vessey 1968), but not second (Thorogood et al. 1992b), case-control study of fatal cardiovascular disease. The higher relative risk estimate for contraceptives containing desogestrel or gestodene, than for levonorgestrel preparations, accords with the results of the key studies of non-fatal venous thromboembolism outlined in Chapter 3 (Bloemenkamp et al. 1995; Jick et al. 1995; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995b; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995c; Spitzer et al. 1996) and with several studies published both before (Andersen et al. 1998; Bennet and Odeberg 1998; Bloemenkamp et al. 1999; Herings et al. 1999; Vasilakis et al. 1999a; Vasilakis et al. 1999b) and after (Jick et al. 2000; Samuelsson and Hagg 2004; Hedenmalm and Samuelsson 2005; Jick et al. 2006) the present research was first published (Parkin et al. 2000). Because of the small number of deaths, the confidence intervals are wide and overlapping. However, it is worth noting that the present research provides additional evidence against the proposed non-causal explanations for the excess risk of venous thromboembolism in users of desogestrel and gestodene oral contraceptives that were discussed in Chapter 3. Referral and diagnostic biases are highly unlikely in a study of fatal events and, following on from the discussion in the previous section, confounding by indication and residual confounding by age seem very unlikely. Of the current pill users, only three of 20 (15.0%) cases and seven of 26 (26.9%) controls were so-called "first-time users" of oral contraceptives; of these, only one case and three controls had been taking the pill for less than a year.

Although based on very small numbers, the present study and the WHO investigation (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995b; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995c) both suggested that oral contraceptives containing cyproterone acetate carried an even greater risk of venous thromboembolism than desogestrel and gestodene preparations. These findings have been confirmed by researchers at the Boston Collaborative Drug Surveillance Program in a nested case-control study based on the UK GPRD (Vasilakis-Scaramozza and Jick 2001) and by researchers in the Netherlands in a population-based case-control study (Rosendaal et al. 2003a). In the former study, the adjusted odds ratio for users of cyproterone acetate oral contraceptives compared with levonorgestrel preparations, was 3.9 (95% CI 1.1 – 13.4) (Vasilakis-Scaramozza and Jick 2001). In the second study, use of cyproterone acetate pills was associated with an 18-fold increase in risk (no confidence interval provided) compared with non-users (Rosendaal et al. 2003a).

Estimates of absolute risk

In the present study, the absolute risk of death from idiopathic pulmonary embolism in women taking oral contraceptives was estimated to be 10.5 (95% CI 6.2 – 16.6) per million woman-years. This is similar to the mortality rates from pulmonary embolism estimated for oral contraceptive users during the 1960s and 1970s. For instance, the mortality rate in users of Enovid in the USA was estimated to be 12.1 per million users (Ad Hoc Committee for the Evaluation of a Possible Etiologic Relation with Thromboembolic Conditions 1963). In the early UK study of cardiovascular mortality in women of child-bearing age, there were 16 deaths from pulmonary embolism among current users of oral contraceptives (Inman and Vessey 1968). Using the two different estimates of oral contraceptive utilisation data provided in the paper, the absolute risk of fatal pulmonary embolism in pill users can be calculated alternately as 23 or 33 per million woman-years. In a subsequent study by the same authors, the annual death rate from pulmonary embolism attributable to the use of oral contraceptives containing 50μg oestrogen was estimated to be 11 per million users (Vessey and Inman 1973). The mortality rate in the Royal College of General Practitioners' Oral Contraceptive Study, based on only three cases, was 28 per million-woman years (Royal College of General Practitioners 1981).

The estimate in the present study was higher than expected based on the incidence of venous thromboembolism among users of modern oral contraceptives reported in the WHO study (1 – 2 per 10,000 users) and a presumed case-fatality rate of 1 – 2% (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995b; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995c). Conversely, a death rate of 14 per million woman-years can be derived from the GPRD study (Jick et al. 1995), although this is based on only six deaths. Incidentally, the present estimate is identical to a predicted rate in users of desogestrel and gestodene contraceptives of 10 per million per year based on calculations undertaken by the Leiden group soon after the key studies were published (Vandenbroucke et al. 1996b).

Overall, the study findings are consistent with the other epidemiological evidence. The estimates of venous thromboembolism mortality based on case-fatality rates are lower than the estimates in the present study, which suggests that the case-fatality of venous thromboembolism in oral contraceptive users may be higher than previously assumed. Certainly estimates from recent population-based studies in the USA suggest that the case-fatality for idiopathic venous thromboembolism is greater than 1 – 2% and may be about 5% (Cushman et al. 2004; Stein et al. 2004).

6.4.2 Biological plausibility

In recent years it has been established that oral contraceptive use is associated with reduced anticoagulant, enhanced procoagulant, and increased antifibrinolytic effects, and that these effects are more pronounced in women taking desogestrel and gestodene preparations (Vandenbroucke et al. 2001). For instance, the initial discovery that users of oral contraceptives containing desogestrel and gestodene had reduced anticoagulant activity secondary to enhanced resistance to activated protein C, when compared with users of other preparations (Rosing et al. 1997; Rosing et al. 1999), has been confirmed in subsequent studies (Alhenc-Gelas et al. 2004; Kemmeren et al. 2004). Moreover, in line with epidemiological findings, it has been shown that resistance to activated protein C is even more marked in users of oral contraceptives containing cyproterone acetate (Alhenc-Gelas et al. 2004). In other studies, additional changes leading to reduced anticoagulant activity, such as decreases in total and free protein S, have also been observed with desogestrel, but not levonorgestrel, oral contraceptives (Tans et al. 2000;

Mackie et al. 2001; Kemmeren et al. 2004). Enhanced procoagulant effects have been demonstrated in a randomised cross-over trial comparing desogestrel and levonorgestrel oral contraceptives; significantly increased prothrombin and factor VII concentrations and decreased factor V levels were observed during the use of the desogestrel preparation (Middeldorp et al. 2000). Finally, in a randomised cross-over trial of desogestrel and levonorgestrel pills, higher levels of thrombin-activatable fibrinolytic inhibitor were measured during use of the desogestrel product (Meijers et al. 2000b).

It has also been confirmed that various inherited thrombophilic abnormalities modify the risk of venous thromboembolism in users of oral contraceptives. For instance, the risk of venous thromboembolism in oral contraceptive users is substantially enhanced in the presence of the factor V Leiden and prothrombin G20210A mutations and with deficiencies of protein C, protein S, and antithrombin (Rosendaal et al. 2003a). Interactions between oral contraceptive use and high levels of factors II and XI (Rosendaal et al. 2003a) and VIII (Bloemenkamp 2005) have also been reported.

6.4.3 Competing interests

Despite the compelling evidence that desogestrel and gestodene pills carry a higher risk of venous thromboembolism than older low-dose preparations, this conclusion has not been universally accepted and for several years members of three groups who undertook earlier research directly funded by the pharmaceutical industry (as discussed in section 3.2.12 of Chapter 3) continued to explore the possibility that the excess risk was explained by various biases. It is notable that this subsequent research was also funded directly (Heinemann et al. 2000; Heinemann et al. 2002; Lidegaard et al. 2002) or indirectly (Farmer et al. 2000b) by industry.

Some of the Transnational investigators, for instance, undertook a second case-control study which they maintained provided "clear evidence that diagnostic suspicion and referral bias does play an important role in case-control studies of venous thromboembolism risk among oral contraceptive users" (Heinemann et al. 2000). Two sets of controls were used in this study: women randomly selected from the general population, and women who were initially suspected of having venous thromboembolism. The odds ratios for current use of any oral contraceptive compared with non-use were 4.33 (95% CI 3.27 – 5.74) in the analysis using population controls

and 2.6 (95% CI 1.75 – 3.88) when the second group of controls was used. Intriguingly, however, no comparisons of risk by types of oral contraceptive were reported and the findings, as presented, do not explain the excess risk associated with the use of desogestrel and gestodene contraceptives found in other studies.

Following a re-analysis of this second case-control study, the investigators went on to argue that the restriction of events to hospitalised and idiopathic cases was an undesirable practice because it resulted in an overestimation the risks associated with contraceptive pills (Heinemann et al. 2002). However, this view was challenged by the findings of a nested case-control study based on a group of women who had been excluded from an earlier study undertaken by the Boston Collaborative Drug Surveillance Program investigators because they had acute clinical conditions such as surgery and lower limb fractures (Jick et al. 2000); it was shown that a failure to exclude such women would, in fact, obscure the true risk associated with oral contraceptives (Black et al. 2002).

The second group of industry-funded investigators used data from the UK GPRD to compare the incidence of venous thromboembolism among pill users before and after the CSM warning in October 1995 (Farmer et al. 2000b). The results were said to be inconsistent with a two-fold excess risk for oral contraceptives containing desogestrel and gestodene. However, the incidence rates were not adequately adjusted for age and other confounders (Skegg 2000b) and the investigators were criticised for conducting a simple time-trend analysis when they had access to detailed data about individual women's exposures and other risk factors (Walker 2000). This failure to adequately address confounding is rather ironic considering that the same group had previously argued that the findings of the key studies were distorted by residual confounding (Farmer et al. 1997a). Moreover, a few months later, the Boston group used the same database to conduct cohort and nested case-control analyses and found a two-fold excess risk in users of desogestrel and gestodene pills relative to users of levonorgestrel preparations in the periods both before and after the CSM announcement (Jick et al. 2000). In addition, it was shown that fewer events occurred after October 1995 than would have been expected had there been no fall in the use of desogestrel and gestodene preparations. Following the publication of the latter research, and a critical editorial

(Skegg 2000b), the editor of the BMJ took the rare action of issuing an apology for an inadequate review of the first study (Smith 2000).

The third group which undertook industry-sponsored research expanded their original Danish case-control study (Lidegaard et al. 1998) to include both women who had events in the subsequent three years and additional controls selected from a population register (Lidegaard et al. 2002). As in the original study, the relative risk estimates were adjusted for duration of use; the odds ratio for desogestrel and gestodene pills compared with low-dose levonorgestrel, norgestimate, and norgestrel products was 1.3 (95% CI 1.0 – 1.8). However, the criticisms of the original study (Walker 1998) still held in relation to the expanded study.

The issue of competing interests attracted further attention following the disclosure that an industry-commissioned study based on the UK GPRD had not been published (Skegg 2000b). This research, which was undertaken in 1997, apparently showed that so-called third generation oral contraceptives carried an excess risk of venous thromboembolism (van Heteren 2001; Weber 2001). Representatives of the manufacturer defended their decision not to publish the findings, claiming that there were methodological problems with the study and that the results added nothing new (Brock 2001). A few months later it was reported that a second industry-funded study also remained unpublished (Sheldon 2001).

Finally, a clear relationship between the source of funding for research and the reported results was highlighted in a meta-analysis based on studies in which data were collected before the CSM warning; the summary adjusted odds ratio of venous thromboembolism in users of "third generation" oral contraceptives relative to "second generation" preparations was 1.7 (95% CI 1.4 – 2.0) (Kemmeren et al. 2001). In an analysis stratified by funding source, the corresponding estimate was only 1.3 (95% CI 1.0 – 1.7) for studies sponsored by the pharmaceutical industry whereas for research which received no such funding it was 2.3 (95% CI 1.7 – 3.2). The results of several other analyses also led the authors to conclude that the excess risk associated with third generation oral contraceptives could not be explained by various biases. First, the summary estimate was unchanged in an analysis restricted to cases in whom the diagnosis was certain. Second, in an analysis stratified by duration of use, elevated

risks were found in both short and longer term users; the odds ratios for use for less than a year and for at least one year were 2.5 (95% CI 1.6 – 4.1) and 2.0 (95% CI 1.4 – 2.7) respectively. Third, the adjusted odds ratio for first-time use of third generation pills compared with first-time use of second generation products was 3.3 (95% CI 2.0 – 5.4).

A second meta-analysis, which included studies with data recorded after October 1995, produced an identical summary odds ratio to the first (1.7 [95% CI 1.3 – 2.1]) (Hennessy et al. 2001). This estimate was reported to be sensitive to a degree of unmeasured confounding, although such a conclusion seems unjustified considering the sensitivity analysis showed that implausibly extreme conditions (the unmeasured confounding factor carried a high relative risk or was very common) would have been required to explain the results of the key studies. Elevated risks were also demonstrated among first-time users in both the first, and subsequent, years of use. Similarly, the association persisted after controlling for duration of use. Interestingly, the authors received financial support from a pharmaceutical company to undertake the meta-analysis, but did not indicate whether they had undertaken an analysis stratified by source of funding (Hennessy et al. 2001)].

6.5 ISSUES SPECIFIC TO PSYCHOTROPIC DRUGS AND VENOUS THROMBOEMBOLISM

6.5.1 Consistency with other studies

Antipsychotic drugs

The finding of an increased risk of fatal pulmonary embolism in current users of conventional antipsychotics is consistent with some (Zornberg and Jick 2000; Thomassen et al. 2001), but not all (Ray et al. 2002), previous studies of non-fatal venous thromboembolism. The observation in the present study that users of low potency formulations carried the highest risk confirms the findings of the nested case-control study based on the UK GPRD which was undertaken by researchers in the Boston Collaborative Drug Surveillance Program (Zornberg and Jick 2000). Unlike that study, however, most of the cases in the present research had been taking their medication for at least a year.

Since this study was published (Parkin et al. 2003), there have been more case reports of venous thromboembolism in users of clozapine (Anil et al. 2003; Pan et al. 2003; Selten and Büller 2003; Yang et al. 2004), olanzapine (Hägg et al. 2003; Waage and Gedde-Dahl 2003; Toki et al. 2004; Bhanji et al. 2005), risperidone (Hamanaka et al. 2004; Zink et al. 2006), conventional antipsychotics (Hamanaka et al. 2004; Matsumoto et al. 2004), and conventional preparations in combination with physical restraint (Laursen et al. 2005). However, it appears that only one further analytical study has directly examined the association between antipsychotics and venous thromboembolism (Liperoti et al. 2005). In this cohort study involving non-schizophrenic people aged 65 years or more who were resident in nursing homes in five states in the USA, users of atypical, but not conventional, antipsychotics had an increased risk of hospital admission with venous thromboembolism. Compared with non-users, the adjusted hazard ratios for people without major risk factors for venous thromboembolism were 4.88 (95% CI 2.03 – 11.72) for current use of clozapine or quetiapine, 2.54 (95% CI 1.69 – 3.82) for risperidone, 1.71 (95% CI 0.96 – 3.45) for olanzapine, 0.96 (95% CI 0.56 – 2.02) for phenothiazines, and 1.04 (95% CI 0.45 – 2.40) for other conventional agents. The estimate for concurrent use of more than one agent was 5.29 (95% CI 2.05 – 13.66). The study differed from previous research in two important respects, which might partly explain an absence of risk for conventional antipsychotics. First, the period of observation was restricted to the first six months of use. Second, the prescribed doses of phenothiazines were said to be substantially lower than those previously associated with venous thromboembolism.

The results of a Danish register-based cohort study published in the same year were also consistent with an increased risk of venous thromboembolism in users of psychotropic drugs (Strudsholm et al. 2005). People who had previously been admitted to a psychiatric hospital with a diagnosis of bipolar disorder, schizophrenia, or anxiety all had an increased risk of pulmonary embolism when compared with sex and age-matched persons without a history of such disorders; the relative risks for the three conditions were 1.61 (95% CI 1.38 – 1.88), 1.78 (95% CI 1.27 – 2.51), and 1.49 (95% CI 1.10 – 2.02) respectively. It is possible that these estimates were distorted by residual confounding by age as the age bands used were extremely wide. It seems highly likely that most people with schizophrenia who were unwell enough to require admission to a psychiatric hospital would have been treated with antipsychotic drugs.

Moreover, it is probable that many patients with bipolar disorder were also prescribed such medicines. Curiously, however, while the investigators concluded that people with mental disorders have an increased risk of venous thromboembolism, they paid scant attention to the possible role of psychotropic drugs.

The previous evidence of an increased risk of non-fatal venous thromboembolism in users of conventional antipsychotics tends to argue against differential survival as an alternative explanation for the results of the present investigation. Moreover, the absence of a significantly increased risk for past use in this study is consistent with the hypothesis that the drugs, rather than any underlying characteristics of the people who used them, were responsible for the increased risk among current users. Nevertheless, the point estimate for past use was elevated, with a wide confidence interval, so the possibility that people who are considered to need these drugs carry some increased risk cannot be ruled out. Earlier studies that found significantly elevated risks for current users of conventional and atypical antipsychotics took past users as the reference group (Walker et al. 1997; Zornberg and Jick 2000). This provided some control for the underlying condition, but it did not permit the evaluation of a possible increased background risk in users of antipsychotic drugs — although it should be noted that no psychiatric or medical conditions were independently associated with an increased risk of venous thromboembolism in the nested case-control study undertaken by the Boston group (Zornberg and Jick 2000).

Recently, it has been proposed that antipsychotic-induced hyperprolactinaemia might be the mechanism by which these drugs increase the risk of venous thromboembolism. In a small laboratory-based study, users of antipsychotics with hyperprolactinaemia had significantly higher levels of platelet stimulation than non-users with normal levels of prolactin (Wallaschofski et al. 2003).

Antidepressant drugs

The observed association between current use of antidepressants and fatal pulmonary embolism is a new finding, although it should be noted that tricyclic drugs (which were most commonly used by the cases) closely resemble the phenothiazines chemically (Potter and Hollister 2001b). In the nested case-control study undertaken by the Boston group, an unadjusted unmatched odds ratio of 1.7 (95% CI 0.8 – 3.7) was obtained for

current use of antidepressants (Zornberg and Jick 2000). This result was based on only three exposed cases and 20 exposed controls, so it was not incompatible with the observation in the present study. However, it should also be borne in mind that the antidepressant users were identified from a cohort of patients who had taken antipsychotic drugs at some time during the study period and such people may be different from other users of antidepressants. Nine cases and four controls were current users of antidepressants in the reanalysis of the Leiden Thrombophilia Study, giving an odds ratio for current use of 2.3 (95% CI 0.6 – 10.2) (Thomassen et al. 2001). Conversely, the adjusted relative risk for current use of antidepressants in the Canadian study based on administrative records was 1.04 (95% CI 0.94 – 1.15) (Ray et al. 2002).

While there have been isolated case reports of venous thromboembolic events in users of selective serotonin reuptake inhibitors since the present research was undertaken (Momen et al. 2003; Kurne et al. 2004), no further analytical studies appear to have been published.

Like antipsychotic users, people taking antidepressants appear to have a higher risk of sudden death than non-users (Mehtonen et al. 1991). Prospective cohort studies have also shown an association between depression and an increased risk of subsequent arterial thrombosis in people without cardiovascular disease at baseline (Anda et al. 1993; Barefoot and Schroll 1996; Pratt et al. 1996; Ford et al. 1998; Ferketich et al. 2000; Roose et al. 2001), and laboratory work has demonstrated enhanced platelet reactivity in people who are currently depressed (Nemeroff and Musselman 2000; Schins et al. 2003). Hence, it is possible that depression itself, rather than the drugs used to treat it, carries an increased risk of venous thrombosis. Indeed, the findings of one laboratory-based study are consistent with such an interpretation and, in addition, they suggest a possible alternative explanation for the preponderance of tricyclic use in the present research. In a randomised double-blind trial, depressed patients with ischaemic heart disease and haematological evidence of platelet activation were randomly allocated to receive a six-week course of a selective serotonin reuptake inhibitor (paroxetine) or tricyclic (nortriptyline) antidepressant (Pollock et al. 2000). The indicators of platelet activation returned to normal in the patients taking paroxetine, but remained elevated in the users of nortriptyline. While these results are intriguing,

the number of participants was very small and such studies involving proxy endpoints should be regarded with caution.

6.6 OTHER RISK FACTORS AND VENOUS THROMBOEMBOLISM

In the present study, current use of hormone replacement therapy was associated with a borderline significant three-fold increased risk of fatal pulmonary embolism. This is consistent with the findings of both observational studies (Boston Collaborative Drug Surveillance Program 1974; Daly et al. 1996; Grodstein et al. 1996; Jick et al. 1996c; Pérez Gutthann et al. 1997; Varas-Lorenzo et al. 1998; Scarabin et al. 2003) and recent randomised controlled trials of hormone replacement therapy (Hulley et al. 1998; Grady et al. 2000; Hoibraaten et al. 2000; Hulley et al. 2002; Writing Group for the Women's Health Initiative Investigators 2002) in which current users had in the order of a two to three-fold increased risk of venous thromboembolism when compared with non-users.

The finding of a significantly increased risk of fatal pulmonary embolism in people with a past history of venous thromboembolism in the present study is compatible with previous research (Goldhaber 2004), as are the findings for a history of superficial venous thrombosis (Kyrle and Eichinger 2005), impaired mobility (Goldhaber 2004), and obesity (Goldhaber 2004).

The observed association between intellectual disability and fatal pulmonary embolism is an interesting finding. There have been isolated case reports of venous thromboembolism in intellectually disabled people with co-morbid medical conditions (Schlichtemeier et al. 1994; Okuyama et al. 2004) or quadriplegia (Lohiya et al. 2005), but it appears that the potential relationship between intellectual disability and venous thromboembolism has not been examined in analytical studies. Indeed, it has been suggested that intellectually disabled people with spastic paraplegia or quadriplegia might be less likely to develop venous thromboembolism, even in the presence of additional risk factors such as fractures and orthopaedic or abdominal surgery, because of increased muscle tone (Rousseau and Guillotel 2001). One of the eight cases with an intellectual disability in the present study was confined to a wheel chair (as a result of spina bifida), although it is possible that the other cases were less active than people

without such disabilities and this might account for the increased risk. Alternatively, it is also possible that the incidence of venous thromboembolism in people with intellectual disabilities is similar to that found in the general population, but the case-fatality rate is higher because of difficulties in recognising and communicating symptoms.

6.7 SUMMARY AND IMPLICATIONS

These are presented in the final chapter, Chapter 12.

PART III FATAL PULMONARY EMBOLISM AND LONG-DISTANCE AIR TRAVEL

CHAPTER 7 VENOUS THROMBOEMBOLISM AND LONG-DISTANCE AIR TRAVEL

7.1 INTRODUCTION

The possible link between long-distance air travel and venous thromboembolism received widespread media attention in late 2000 and 2001. This interest appears to have been generated by at least three events. The first, in October 2000, was the death from pulmonary embolism of a 28 year old woman shortly after disembarking from a flight from Australia to the UK (BBC News 2000a). Media reports of this event were soon followed by accounts of other people who had developed venous thromboembolism following long-distance air travel (Ferguson 2000; Derbyshire and Dutter 2001; Espiner 2001a).

The second factor which stimulated media interest was the publication in October and November 2000 of the results of two studies (Bendz et al. 2000; Kraaijenhagen et al. 2000), and the pre-publication release of the findings of another (BBC News 2000b). In the first study to be published, a case-control design, travel by air and by other means of transport was not associated with an increased risk of deep vein thrombosis (Kraaijenhagen et al. 2000). In the second, an uncontrolled experiment, activation of the coagulation system was found in volunteers who were exposed to hypobaric hypoxic conditions similar to those encountered during flight (Bendz et al. 2000). Finally, in a randomised controlled trial of graduated compression stockings in volunteers, 10% of the control group were said to have had ultrasonic evidence of asymptomatic deep vein thrombosis following a flight of more than eight hours (Scurr et al. 2001). The media reports about the conflicting results of these studies (BBC News 2000b; BBC News 2000c; BBC News 2000d) were followed by various reports of the "thousands" of deaths from pulmonary embolism which could be attributed to long-distance flights each year (BBC News 2001a).

The third event which attracted media attention was the release, in November 2000, of a report by the UK House of Lords Select Committee on Science and Technology entitled *Air Travel and Health* (House of Lords Select Committee on Science and Technology 2000). In reviewing the current knowledge about the health implications of air travel,

the Committee had examined a broad range of issues such as cabin ventilation, air quality, noise, stress, deep vein thrombosis and other medical conditions, the management of in-flight medical emergencies, and the adequacy of information provided to passengers. However it was the discussion about deep vein thrombosis which received the most publicity (Ferriman 2000; Laurance 2000). The Committee concluded that the risk of developing deep vein thrombosis in relation to air travel appeared to be "exceedingly small" for healthy people, while for passengers with pre-existing risk factors, it was considered that "there may be an additional risk from flying, but it is not currently quantifiable". Given this "paucity of data" on air travel and venous thromboembolism, the Committee recommended that the Department of Health commission a case-control study to investigate the potential link as soon as possible, and that in the meantime airlines and travel agents should provide prospective passengers with information about simple measures to minimise the risk of developing flight-related deep vein thrombosis. The Committee also criticised the use of the term "economy class syndrome" and suggested that "traveller's thrombosis" was a more appropriate expression.

The ensuing months saw several developments. WHO convened a meeting in March 2001 which was attended by several researchers with an interest in venous thromboembolism, as well as representatives of airline companies, the International Air Transport Association, the International Civil Aviation Organization, the European Commission, and various consumer groups (Mendis et al. 2002). The meeting participants concluded that there was probably a link between air travel and venous thromboembolism, and that it was most likely to occur in passengers with other risk factors for venous thromboembolism, but there were insufficient data to quantify the risk. In response to the need for further information, it was agreed to initiate several new studies under the auspices of WHO and the International Civil Aviation Organization.

Advice for air passengers were subsequently issued by WHO (World Health Organization 2005) and by health departments in several countries, including the Department of Health in the UK (Department of Health 2001) and the Ministry of Health in New Zealand (Medsafe 2001a). In Australia the Federal Government launched an enquiry into the risks of long-haul flights (Gallus and Baker 2001). There

were reports of proposed litigation against airlines by people who had developed venous thromboembolism after a long-distance flight (Espiner 2000; AAP 2001), at least one travel insurance company took the opportunity to attract business by assuring prospective customers that the costs of treating flight-related venous thromboembolism would be covered by their policy (Yoon 2001), the use of various devices were promoted as providing some protection against venous thromboembolism (Caruana et al. 2003), and travel medicine clinics in South Africa and the USA offered screening for prothrombotic genetic mutations (Bateman 2003).

Some airlines were reportedly reluctant to acknowledge the potential association between air travel and venous thromboembolism (Espiner 2001b), but did provide advice to passengers about measures they could undertake to prevent the condition (Air New Zealand 2001; BBC News 2001b). The airline industry was criticised by some people who maintained that the risk of venous thromboembolism in air travellers had been recognised for decades and that the airlines had failed to do anything about it (BBC News 2001c).

However, was there really sufficient evidence to conclude that air travel increased the risk of venous thromboembolism? The first review of the topic in 1992 concluded that although the published data were suggestive of a link between air travel and venous thromboembolism, in the absence of any analytical epidemiological studies it was impossible to draw any definite conclusions about the association (Milne 1992). Other reviews published before the media furore, also reported that the evidence for a link was largely circumstantial (Forbes and Johnston 1998; Giangrande 2000; Kesteven 2000).

Since 2000, the potential association between air travel and venous thromboembolism has been the subject of many studies. This chapter will examine the data that were available before the publication of the research outlined in Chapters 8 – 11 (Parkin et al. 2006) and will attempt to answer the following questions:

1. Is there an association between air travel and venous thromboembolism? And if so,
2. Is it likely to be causal? And if so,
3. Do other risk factors for venous thromboembolism modify the risk?

4. What is the incidence of flight-related venous thromboembolism?
5. What are the possible causal mechanisms?

To identify relevant papers, the Medline database was searched using the following terms: "pulmonary embolism" "thromboembolism", "venous thrombosis", "thrombophlebitis", "travel", and "aircraft". Terms used to search the Embase database included "venous thromboembolism", "thromboembolism", "vein thrombosis", "lung embolism", "deep vein thrombosis", "travel", "aviation", "flight", and "flying". The reference lists of retrieved papers were also examined.

Although several authors have described cases of arterial thrombosis following prolonged travel (Collins et al. 1979; Teenan and McKay 1992; Ashkan et al. 1998), the discussion in this chapter will be confined to venous events.

7.2 IS THERE AN ASSOCIATION BETWEEN AIR TRAVEL AND VENOUS THROMBOEMBOLISM?

7.2.1 Case reports and case series

The first intimation that travel might increase the risk of venous thromboembolism came in 1954 when a Boston surgeon described five cases of deep vein thrombosis which he attributed to prolonged sitting (Homans 1954). Four of the patients had recently undertaken long journeys by air (two) or car (two), and the fifth developed symptoms after leaving the theatre. The author proposed that people should undertake leg exercises when seated for long periods and advised doctors to be suspicious of calf pain that developed after travel and other situations involving prolonged sitting.

Since this paper appeared, at least 45 case reports and case series have been published which describe almost 700 cases of venous thromboembolism among air travellers, some of which were fatal. In addition, several of the case series included people who developed venous thromboembolism following travel by car and other modes of transport. These accounts of venous thromboembolism following air and other travel are reviewed in detail in the table in Appendix C, but a few remarks will be made here to summarise the main findings.

First, the duration of air travel undertaken by the cases ranged from less than three hours to more than 30 hours. Second, some of these flights were undertaken in economy class and some in first or business class. Ironically in one case series entitled *Air travel and thrombotic episodes: the economy class syndrome* one of the cases (also an author) travelled in business class (Cruickshank et al. 1988). Another report described the occurrence of deep vein thrombosis in a President of the USA following a long-distance flight on the presidential aircraft in 1974 (Barker et al. 1997). Such examples clearly highlight the misleading nature of the term "economy class syndrome".

Third, while some authors confined their attention to people who developed symptoms during a flight or when disembarking (Beighton and Richards 1968; Thomas et al. 1981; Bürki 1989; Clerel and Caillard 1999; Partsch 2001; Tan et al. 2002; O'Connell et al. 2005), others included events which occurred up to six weeks after air travel (Eklof et al. 1996). The immediate onset of symptoms was thought by some to provide compelling evidence that fresh thrombus had formed on the flight (Ledermann and Keshavarzian 1983). This theory was supported by the findings of a necropsy study of people who died following a long-distance flight — although it was also revealed that in a minority of cases, pulmonary emboli had been present before the index flight (Cheung and Duflou 2001). The latter finding was consistent with reports that some cases had developed symptoms after an outbound flight, but were not diagnosed until after subsequent flights (Kesteven and Robinson 2001). Several cases had symptoms which were mild and did not develop until some time after a flight, leading to delays in diagnosis (Voorhoeve and Bruyninckx 1990; Emonson 1997). Others had atypical symptoms which initially attracted alternative diagnoses (Holliday 1985; Black 1993). Yet others had symptoms of pulmonary embolism which at first were attributed to myocardial infarction (Sinzinger et al. 1999).

Fourth, the characteristics of cases varied between reports with respect to age, the ratio of males to females, and the proportion of cases with pre-existing risk factors for venous thromboembolism. These variations may partly be explained by the methods used to select patients for review. Some series included consecutive patients while others did not, some included patients in general hospitals while others described the patients admitted to military hospitals, and yet others included outpatients attending specialist thrombosis centres. The differences in characteristics can also be attributed to the

various methods used to obtain information about air travel and other risk factors for venous thromboembolism. Some authors undertook retrospective reviews of medical records and the data obtained were therefore dependent on both the questions that the patients had been asked and the information they had spontaneously volunteered. Even data that were sought prospectively were not always comprehensive — for example, the use of oral contraceptives (Benoit 1992) and hormone replacement therapy (Paganin et al. 1996) by female passengers was not enquired about until surprisingly recently.

Fifth, in studies of consecutive patients with venous thromboembolism varying proportions of patients were identified as recent air travellers. This may be due to the reporting and recording biases inherent in retrospective reviews of medical records, as well as differences in the underlying frequency of long-distance air travel in the source populations.

Finally, a few studies ascertained the seating position of the cases (for example, whether or not they had an aisle seat) and studied their in-flight behaviour (for example, whether they moved about the cabin or undertook seated leg exercises, and whether they consumed alcohol or took sedatives during the flight) (Sinzinger et al. 1999; Parsi and McGrath 2000; Parsi et al. 2001). Some also ascertained whether the cases were passengers or crew (Parsi and McGrath 2000; Parsi et al. 2001).

While these case reports and case series are suggestive of a link between air travel and venous thromboembolism, they provide only circumstantial evidence. In addition to the selection and information biases already discussed, one of the major limitations of these data, as with all case reports and case series, is the lack of a comparison group. Without such a group it is impossible to know whether venous thromboembolism occurs more often in air travellers than in non-travellers, and whether air travellers who develop the condition have more pre-existing risk factors than other passengers. To explore these questions, it is necessary to turn to analytical epidemiological studies. Unfortunately, however, surprisingly few such studies have explored the potential association between air travel and venous thromboembolism. Moreover, much of the research suffers from considerable methodological problems. In the following sections, therefore, these investigations are considered in some detail.

7.2.2 Case-control studies

Only eight case-control studies had examined the association between travel by air (and other modes of transport) and venous thromboembolism before the publication of the research outlined in Chapters 8 – 11 (Parkin et al. 2006). These investigations are first summarised in Table 7.1 and then discussed individually. As will be seen, the studies differed in their definitions of travel (travel by any mode of transport, or by air alone), the duration of the journey, the designated period of risk following a journey, the venous thromboembolic events that were included, the methods that were used to confirm the diagnosis, the exclusion criteria that were employed, and the approaches towards the selection of controls.

Table 7.1 Case-control studies of travel and venous thromboembolism

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information	Odds ratio (95% CI)	Comments
(Ferrari et al. 1999)	160 cases, 160 controls	All patients with VTE admitted to the cardiology department of a Nice hospital between July 1992 and August 1995 (except 8 patients who died after admission). Confirmation of DVT: Doppler US, unclear whether staff were blinded to travel history. Confirmation of PE: not specified.	Age-matched consecutive patients admitted to the same cardiology department with a first admission for another cardiovascular condition. Unclear whether individual or frequency matching.	Interviewer-administered questionnaire in hospital. Travel exposure Journey > 4 hours by aeroplane, car, train, or boat in 4 weeks *before admission.* Reference category "Non-travellers" (people who did not undertake travel as above).	**Unadjusted unmatched OR** Any travel > 4 hours 3.98 (1.9 – 8.4)	1. Exclusion criteria inconsistently applied. 2. Participation rate of controls not given. 3. Choice of control series may have led to an overestimation of risk. 4. Date of admission nominated as index date. 5. Cases interviewed twice, relatives assisted. 6. Unmatched analysis 7. Potential confounding was not explored.
(Samama and the Sirius Study Group 2000)	***Overall study population*** 636 cases, 636 controls ***Medical study population*** 494 cases, 494 controls	***Overall study population*** Patients with DVT who presented to GP centres in France October 1990 – December 1991. ***Medical study population*** Above patients excluded if surgery or lower limb plaster cast ≤ 3 weeks before admission. Confirmation of DVT: duplex US, B-mode US, venography, and / or impedance plethysmography.	First patient after case who presented with an influenzal or rhinopharyngeal condition. Matched by GP centre, sex and age (10-year age bands).	Standardised data form, unclear whether completed by GPs or researchers. Travel exposure "Long-distance travel" ≤ 3 weeks *before GP visit.* Duration and mode of transport not defined. Reference category "Non-travellers" (people who did not undertake travel as above).	**Adjusted unmatched OR** ***Overall study population*** Not reported. ***Medical study population*** "Long-distance travel" 2.35 (1.45 – 3.80) OR adjusted for sex and age.	1. 102 confirmed cases excluded because of missing data or inadequate matching. 2. Participation rates of other cases and controls not given. 3. Choice of control series may have led to over- or underestimation of risk. 4. Date of GP visit nominated as index date. 5. Unmatched analysis, adjusted for 2 of the matching factors. 6. Potential confounding by other factors was not explored.

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information	Odds ratio (95% CI)	Comments
(Kraaijenhagen et al. 2000) (First DVT study) (ten Wolde et al. 2003) (Pooled analysis)	***First DVT study*** 186 cases, 602 controls ***Pooled analysis*** 244 cases with DVT, 714 controls 233 cases with PE, 756 controls	***First DVT study*** Consecutive outpatients > 18 years who presented with clinically suspected DVT between April 1997 and January 1999, objective evidence of DVT or PE. Confirmation of DVT: D-dimer, compression US or contrast venogram. Confirmation of PE (symptomatic patients only): D-dimer, V-Q scan or pulmonary angiogram. Investigations conducted by staff blinded to travel history. ***Pooled analysis*** Above patients, plus patients fulfilling the same criteria who presented between February 1999 and September 2000. Also inpatients and outpatients presenting with clinically suspected PE between October 1998 and September 2000, objective evidence of PE.	***First DVT study*** Consecutive outpatients > 18 years who presented with clinically suspected DVT (during the same period as the cases) who had no objective evidence of DVT or PE. ***Pooled analysis*** Consecutive outpatients > 18 years who presented with clinically suspected DVT or PE (during same period as cases) who had no objective evidence of DVT or PE.	***First DVT study*** Questionnaire before diagnostic investigations, unclear whether self or interviewer-administered. Travel exposure Journey > 3 hours by car, train, boat, or aeroplane, in 4 weeks *before presentation.* Reference category "Non-travellers" (people who did not undertake travel as above).	**Unadjusted OR** ***First DVT study*** Any travel > 3 hours 0.7 (0.3 – 1.4) Any travel > 5 hours 0.4 (0.1 – 1.3) Air travel > 3 hours 1.0 (0.3 – 3.0) ***Pooled analysis*** Any travel > 3 hours 0.9 (0.6 – 1.4) Obtained similar results when excluded those unlikely to have travelled. Any travel 11 – 15 hours 2.5 (1.0 – 6.2) Any travel > 16 hours 1.3 (0.4 – 4.3) Air travel > 3 hours 1.2 (0.7 – 2.1)	***First DVT study*** 1. Lack of power. 2. Researchers based in the Netherlands and Italy, but the specific source(s) of the cases and controls was not given. 3. Participation rates of cases and controls not given. 4. Choice of control series may have led to an underestimation of risk. 5. Date of presentation nominated as index date. ***Pooled analysis*** As in 2 – 5 above.

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information	Odds ratio (95% CI)	Comments
(Dimberg et al. 2001)	81 cases, 891 controls	Identified from medical insurance claims for venous thrombosis by World Bank staff who were employed in Washington and had medical insurance between 1995 and 1998.	Randomly selected from records of World Bank staff with medical insurance and employed in Washington 1995 – 1998.	Travel exposure Record of completing an international mission ≤ 30 days *before medical insurance claim filed.* Reference category No record of completing international mission ≤ 30 days before index date.	**Adjusted OR** Recent mission 0.89 (0.39 – 2.02) OR adjusted for sex and age.	1. Diagnosis not confirmed by reference to personal medical files. 2. May have missed some cases if they delayed submitting claims.
(Arya et al. 2002) (Original analysis) (Arya and Cohen 2003) (Reanalysis)	185 cases, 383 controls	Consecutive outpatients aged 16 – 93 years with clinically suspected DVT who were referred by GPs and hospital emergency department staff to the DVT Clinic at King's College Hospital in London between February 2000 and June 2001, objective evidence of DVT. Confirmation of DVT: duplex US. Not stated whether staff were blinded to travel history.	Consecutive outpatients with clinically suspected DVT who were referred to the DVT Clinic (during the same period as the cases) who had no objective evidence of DVT.	Interviewer-administered questionnaire. Travel exposure Air or "surface" journey > 3 hours in 4 weeks *before presentation.* Reference category "Non-travellers" (people who did not undertake travel as above).	**Unadjusted OR** ***Original analysis*** Any travel > 3 hours 1.4 (0.7 – 2.6) Air travel > 3 hours 1.2 (0.6 – 2.3) Air travel > 8 hours 1.3 (0.6 – 2.8) ***Reanalysis*** Any travel > 3 hours, ≥ 1 risk factor 2.9 (1.1 – 7.9) Any travel > 3 hours, no risk factors 0.7 (0.2 – 2.2)	***Original analysis*** 1. Participation rates of cases and controls not given. 2. Choice of control series may have led to an underestimation of risk. 3. Date of presentation at DVT Clinic nominated as index date. 4. Potential confounding was not explored. ***Reanalysis*** 1. As in 1 – 4 above. 2. Number of controls reported to have risk factors inexplicably different from original analysis.

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information	Odds ratio (95% CI)	Comments
(Hosoi et al. 2002)	101 cases, 106 controls	Consecutive patients with clinically suspected DVT who were referred to the vascular laboratory at Ealing Hospital in London between April 2000 and June 2001 and were found to have objective evidence of DVT. 36 patients were excluded because they had no opportunity to travel. Confirmation of DVT: duplex US Investigations conducted by staff blinded to travel history.	Consecutive patients with clinically suspected DVT who were referred to the same vascular laboratory between April and June 2001 who had no objective evidence of DVT. 28 patients excluded because they had no opportunity to travel.	Interviewer-administered questionnaire. Travel exposure Journey > 3 hours by any mode of transport in 2 weeks *before onset of symptoms*. Reference category "Non-travellers" (people who did not undertake travel as above).	**Unadjusted OR** Any travel > 3 hours 1.3 (0.6 – 2.8) Air travel > 3 hours 0.8 (0.3 – 1.9)	1. Participation rates of cases and controls not given. 2. Choice of control series may have led to underestimate of risk. 3. Controls selected during final 3 months of 15-month study — coincided with a period of intense media interest in the possible link between air travel and VTE. 4. Potential confounding was not explored.

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information	Odds ratio (95% CI)	Comments
(Martinelli et al. 2003)	210 cases, 210 controls	Consecutive patients aged 20 – 70 years referred to a thrombosis centre between January 1999 and September 2001 for thrombophilia screening following a first diagnosis of proximal DVT or PE at some time in the previous 24 months. Patients with known malignancy were excluded. Confirmation of DVT: Doppler US or venography. Confirmation of PE: V-Q scan, computed tomography, or pulmonary angiography. Not stated whether investigations were conducted by staff blinded to travel history.	Matched by age (10-year age bands), sex and educational level, and selected from a group of volunteers who had undergone thrombophilia testing during the study period (friends or partners of all patients referred to the thrombosis centre). Potential controls were excluded if they had a personal history of venous thrombosis or overt malignancy.	Interviewer-administered questionnaire. Travel exposure Air travel in month before VTE event (cases) or visit to thrombosis centre (controls). Reference category "Non-travellers" (people who did not undertake travel as above).	**Unadjusted unmatched OR** Any air travel 2.1 (1.1 – 4.0) Air travel > 8 hours 3.0 (0.9 – 9.5) Any air travel with thrombophilia 16.1 (3.6 – 70.9) Any air travel with OC use 13.9 (1.7 – 117.5) **Adjusted unmatched OR** Any air travel with thrombophilia 16.8 (3.8 – 74.7) OR adjusted for sex, age, and BMI. Any air travel with OC use 23.4 (2.6 – 211.2) OR adjusted for age and BMI.	1. Median time of 5 months (range 1 – 24) elapsed between VTE event and the date of interview for cases, whereas controls were asked about risk factors in the month leading up to their interview. 2. Unmatched analysis, adjusted for 2 of the matching factors (sex and age), but not the third (education). 3. Potential confounding by other factors was not considered.

Reference	Number of participants	Selection of cases	Selection of controls	Exposure information	Odds ratio (95% CI)	Comments
(Rosendaal 2002) (Interim results) (Cannegieter et al. 2006)	1,906 cases, 1,906 controls	Consecutive patients < 70 years with a first episode of VTE who were registered for anticoagulation treatment at 6 regional anticoagulation clinics in the Netherlands between March 1999 and May 2002. Excluded patients unable to complete questionnaire, those who died soon after VTE event, people in end stage of a disease. Case-only analysis based on 1,025 women < 50 years. Reviewed diagnosis of DVT and PE in sample of cases, fulfilled criteria for Dutch diagnostic standard in 97% DVT and 78% PE cases respectively. Not stated whether investigations were conducted by staff blinded to travel history.	Spouses of 1,867 cases, served as a control to their own husband or wife. Spouses of 229 cases who had been deemed ineligible matched by sex and 5-year age groups to 229 of 557 cases whose spouses did not want to participate. Same exclusion criteria as cases.	Self-administered questionnaire, or interview by telephone (but did not ask questions about travel). Travel exposure Journey ≥ 4 consecutive hours by any mode of transport in 8 weeks *before index date* (date of event). Reference category "Non-travellers" (people who did not undertake travel as above).	**Unadjusted matched OR** VTE, any travel > 4 hours 2.1 (1.5 – 3.0) VTE, any travel 4 – 8 hours: 2.0 8 – 12 hours: 1.8 > 12 hours: 2.8 VTE, air travel > 4 hours 1.7 (1.0 – 3.1) DVT, any travel > 4 hours 1.9 (1.1 – 3.2) DVT, air travel > 4 hours 3.0 (1.3 – 7.1) Interactions with FVL, BMI > 30 kg/m², height < 1.60m or > 1.90m, OC use.	1. Only 78% of sample of PE diagnoses confirmed according to Dutch diagnostic standards. 2. 3,902 cases of VTE met initial eligibility criteria, only 1,906 (48.8%) included in study. 3. 190 case/control pairs excluded because one or both members gave information about travel *after* rather than *before* the index date. 4. 233 cases and 182 controls had travelled but analyses based on 98 cases and 47 controls because of concordance in positive exposure status in 135 case/control pairs. 5. Possibility that relative risk underestimated because of 8-week risk period. 6. Undertook matched analysis, but did not explore confounding by other factors.

Abbreviations used in the table BMI: body mass index, DVT: deep vein thrombosis, FVL: factor V Leiden, GP: general practitioner, OC: oral contraceptive, OR: odds ratio, PE: pulmonary embolism, US: ultrasound, V-Q scan: ventilation-perfusion scan, VTE: venous thromboembolism.

Ferrari et al (1999)

This French hospital-based case-control study, which involved 160 cases and 160 controls, was the first analytical study to examine the association between travel and venous thromboembolism (Ferrari et al. 1999). Travel (by air, car, train, or boat) of more than four hours' duration in the four weeks before admission with deep vein thrombosis or pulmonary embolism was associated with a significant four-fold increase in risk (unadjusted odds ratio 3.98 [95% CI 1.9 – 8.4]).

There were several sources of selection and information bias in this study. An age-matched control group was reportedly selected from consecutive patients with other cardiovascular conditions who were admitted to the same cardiology department as the cases. Apparently all cases, apart from eight who died after admission, were included in the study. However, it is unclear whether all of the eligible controls participated. The events that led to the admission of the controls were chest pain (76%), arterial hypertension (13%), and syncope (11%). The preponderance of patients with chest pain resulted in a greater proportion of men in the control group (66.2% c.f. 51.8% of cases) and a potentially biased sample with respect to travel exposure. While only those with a first admission owing to a cardiovascular event were selected as controls, it is nevertheless possible that some of these patients experienced prodromal symptoms in the weeks before admission and were therefore less likely to travel than the cases. Hence, because the admission date of each case and control (rather than the date the symptoms began) was taken as the index date, any association between travel and venous thromboembolism might have spuriously been strengthened. Conversely, it is also possible that the magnitude of any travel effect was underestimated since the exclusion criteria seem to have been applied inconsistently in this study. Patients with "severe diseases that might have limited their mobility" were excluded from the control group, as were patients who had been treated with anticoagulant or antiplatelet drugs. Yet it appears that these same criteria were not applied to the cases, since 79 patients had known cancer or had developed thrombosis following bed rest or surgery.

An interviewer-administered questionnaire was used to obtain information from cases and controls about known and suspected risk factors for venous thromboembolism, including travel. Cases were interviewed at their bedside within the first few days after admission and the interview was repeated immediately before discharge, often with the

assistance of next of kin. It is not clear whether controls were also interviewed twice, nor is it obvious whether their relatives were involved. Any failure to follow an identical protocol for controls might have resulted in a less accurate ascertainment of travel history and could have led to a biased estimate of true risk. It is also not apparent whether the diagnostic investigations were undertaken before the cases were interviewed and whether the radiology staff were blinded to exposure status.

Although the researchers collected extensive information about risk factors for venous thromboembolism (the questionnaire comprised more than 300 questions and included enquiries about recent surgery, bed rest, pregnancy, venous trauma, use of oral contraceptives or hormone treatment, known cancer, systemic disease, and known coagulation abnormalities), they failed to explore the possibility of confounding. This is surprising since they did note that cases were less likely to be male, more likely to be obese, and more likely to have a history of deep vein thrombosis than controls. Furthermore, as some commentators observed, the conditions with which the controls were admitted occur more often among people in lower socio-economic groups (MacGillavry et al. 2001). Since such people would be less likely to have travelled, it is possible that socio-economic status might have confounded the association between travel and venous thromboembolism, leading to an overestimation of the odds ratio. Nonetheless, the researchers simply reported a crude odds ratio. Moreover, they did not advise whether matching by age was undertaken at an individual level or whether frequency matching was employed. If the former approach was used, then age should have been accounted for in the analysis to avoid a conservative bias in the estimate of relative risk (Rothman and Greenland 1998).

Samama and the Sirius Study Group (2000)

In this French case-control study, which examined a number of risk factors for deep vein thrombosis among general practice patients, a significant two-fold increased risk of venous thrombosis was found for people who had undertaken long-distance travel (not defined) in the three weeks before diagnosis (Samama and the Sirius Study Group 2000). In an analysis based on 494 cases and 494 controls, the sex and age-adjusted odds ratio for long-distance travel was 2.35 (95% CI 1.45 – 3.80).

Selection and information biases may have played a role in this study. Of a total of 738 confirmed cases, 102 (13.8%) were excluded because of missing data or inadequate matching. Hence, a total of 636 cases were included, although the key analyses were based on a sub-group (referred to as the medical study population, *n = 494*) who had not undergone surgery or had a lower limb plaster cast applied in the three weeks before diagnosis. The overall participation rate of cases was not given.

One control, matched by general practice, sex, and age, was selected for each case; general practitioners were asked to include the first patient of the appropriate sex and age who presented with influenza or a rhinopharyngeal condition following the identification of the case. Although it is unclear whether the doctors were provided with more detailed instructions, it is unlikely that they would have consciously manipulated the selection of controls according to travel exposure since the study was concerned with a broad range of risk factors for deep vein thrombosis. It is possible, however, that the general practitioners might have excluded sicker patients, who would have been less likely to travel, if inclusion in the study meant that controls would be subjected to a long interview. Any such bias would tend to lead towards an overestimation of the prevalence of travel in the population that gave rise to the cases and hence an underestimation of relative risk. Unfortunately there was no information provided about the participation rate of the controls.

The selection of patients with influenza or rhinopharyngeal conditions as controls might have led to a biased estimate of relative risk if these complaints were associated with the likelihood of travel. For example, certain groups of people, such as smokers and people with chronic illnesses, are more at risk of respiratory infections and may also be less likely to travel. These people are also more likely to belong to lower socio-economic groups, further reducing the possibility of travel. Thus, any association between venous thromboembolism and air travel might have been overestimated. It is also possible that people who intended to travel delayed or postponed their journey following the onset of influenza or rhinopharyngeal symptoms. This is an issue because the date of the visit to the general practitioner was taken as the index date, rather than the date of onset of the symptoms. Conversely, if recent travellers were more likely to have contracted a respiratory infection than people who had not travelled, then the association between travel and venous thromboembolism might have been underestimated. The possibility

of a selection bias was raised by the researchers in relation to the surprising lack of an association between oral contraceptive use and venous thromboembolism (odds ratio 0.60, p = 0.08) and an apparent protective effect of smoking (odds ratio 0.66, p-value < 0.04). They attributed these findings to the fact that smokers were more likely to present with respiratory conditions and thus be selected as controls, and smoking was strongly associated with oral contraceptive use among the female controls.

For each case and control, a standardised form was used to record demographic data and information about 23 permanent (or intrinsic) risk factors for deep vein thrombosis and 24 triggering events in the three weeks before diagnosis. In the medical study population, 85.2% of cases and 53.4% of controls were reported to have one risk factor for deep vein thrombosis, and 56.7% and 18.4% respectively had two or more risk factors. It appears that an unmatched analysis was undertaken, with adjustment for two of the matching factors (sex and age). The researchers reported that it was not possible to adjust for any other potential confounders in a multivariate regression model because of a large number of interaction tests that were statistically significant.

Kraaijenhagen et al (2000)

This study, which was undertaken by researchers in the Netherlands and Italy, included 186 cases and 602 controls (Kraaijenhagen et al. 2000). Air travel of more than three hours' duration in the four weeks before diagnosis was not associated with an increased risk of deep vein thrombosis; the unadjusted odds ratio was 1.0 (95% CI 0.3 – 3.0). The unadjusted estimate for travel by any form of transport (air, car, bus, train, or boat) was 0.7 (95% CI 0.3 – 1.4). Cases were more likely than controls to have had a previous episode of venous thromboembolism (22% cases, 10% controls), to have a known malignancy (22% cases, 10% controls), and to have recently undergone surgery (26% cases, 13% controls), but were less likely to have suffered recent trauma (11% cases, 16% controls). Adjustment for these risk factors, age, and for the duration of symptoms reportedly had no impact on the odds ratios. The inclusion of people with such risk factors was criticised on the grounds that malignancy, recent surgery or trauma might have reduced the likelihood of travel (Ferrari and Morgan 2001), however the estimate for recent travel by any means did not change when such cases and controls were excluded (odds ratio 0.5 [95% CI 0.2 – 1.6]). Neither was an elevated risk found for any travel of more than five hours' duration (odds ratio 0.4 [95% CI 0.1 – 1.3]).

Only four of the 186 cases (2.2%), and an identical proportion of controls, had undertaken air travel and the duration of their flights were not reported. This led to criticisms that the study might have been underpowered to detect an elevated risk (Burnand et al. 2001; Reele 2001). This would be especially so if the cases undertook relatively short flights, since (as will be discussed later) it seems there is a dose-response relationship between flight duration and the incidence of venous thromboembolism (Lapostolle et al. 2001; Perez-Rodriguez et al. 2003). In response, the researchers reported the median duration of travel by any mode of transport, but did not provide any details about the duration of air travel (Kraaijenhagen and Büller 2001). They also acknowledged that the upper bound of the 95% confidence interval for air travel (3.0) was not inconsistent with an elevated risk and indicated that they had extended their study to include more cases of deep vein thrombosis (outpatients referred between February 1999 and September 2000) and patients with pulmonary embolism (outpatients and inpatients referred between October 1998 and September 2000).

The results of the extended study were reported in 2003 (ten Wolde et al. 2003). The data were pooled to explore the risks associated with any travel, travel by particular modes of transport, and the duration of travel. In one analysis, patients who were unlikely to have travelled (those with a malignancy or with a history of recent surgery, trauma, immobilisation, or a hospital admission) were excluded. The only elevated risk was observed for travel by any means of 11 – 15 hours' duration (odds ratio 2.5 [95% CI 1.0 – 6.2]). The odds ratios for travel of more than 16 hours by any means and for air travel of more than 3 hours were 1.3 (95% CI 0.4 – 4.3) and 1.2 (95% CI 0.7 – 2.1) respectively.

There is a strong possibility that selection biases inherent in this study led to an underestimate of any association between travel and deep vein thrombosis. The investigators reported that they tried to minimise potential referral biases by taking as their control group all people with clinically suspected deep vein thrombosis who were referred for investigation and were subsequently found to have no evidence of the condition. However the selection of controls from a group of patients initially suspected of having the disease of interest is only appropriate in situations where the exposure of interest does not produce similar symptoms to the outcome of interest (Rosendaal et al. 2003b). But, as several commentators observed, travellers might have been more prone

to benign leg swelling or discomfort than non-travellers, and moreover doctors might have been more likely to refer patients with symptoms suggestive of deep vein thrombosis if they had travelled (Cates 2001; MacGillavry et al. 2001; Rosendaal et al. 2003b). Because patients with benign symptoms would have subsequently been assigned to the control group, this might have resulted in an overestimation of the prevalence of travel in the population that gave rise to the cases and an underestimation of any association between travel and deep vein thrombosis. The researchers replied that such a scenario was unlikely because patients were referred for investigation, on average, seven days after the onset of symptoms and in most patients the symptoms were unilateral (Kraaijenhagen and Büller 2001). However, they did not indicate whether this was also true for the air travellers, or indeed whether there were any differences between cases and controls in relation to the nature of their symptoms and the time which had elapsed since the onset of their symptoms.

In their later extended study, the researchers reported elevated relative risks for malignancy (odds ratio 2.6 [95% CI 1.8 – 3.9]) and recent surgery (odds ratio 2.4 [95% CI 1.6 – 3.7]) which they cited as evidence against any referral bias (ten Wolde et al. 2003). This argument does not consider the possibility that patients with symptoms suggestive of deep vein thrombosis might be more likely to present themselves to their doctor if they had recently flown, than if they had cancer or had recently undergone surgery, since the public are probably more aware of the possible link between air travel and venous thromboembolism.

The researchers gave no information about the participation rates of the cases and controls. An additional issue is that some cases might have been misclassified as controls if they delayed seeking attention for their symptoms and hence allowed time for a thrombus to spontaneously lyse (Reele 2001) — such misclassification would result in an underestimation of any association between air travel and venous thromboembolism. Since patients presented *on average* a week after the onset of their symptoms, this is not implausible. It has also been suggested that people with thrombosis in the deep veins of the calf might have been misclassified as controls because compression ultrasonography is an inaccurate technique for detecting such thromboses (Burnand et al. 2001). Finally it is also possible that air travel by some of the subjects was not identified because the date that patients were referred was nominated as the index date.

In summary then, a lack of power, a likely selection bias, the potential misclassification of cases as controls, and the possibility of uncontrolled confounding would all have tended to bias the estimate of relative risk towards the null value and may explain the absence of an association in this study.

Dimberg et al (2001)

In this case-control study, based on the medical insurance records of World Bank staff, who were employed in Washington and insured between 1995 and 1998 (*n= 8,189*), no association was found between recent air travel and the risk of venous thrombosis (Dimberg et al. 2001). The study was prompted by an observed increase in health insurance claims by World Bank employees for venous thrombotic disorders in 1997. After adjusting for sex and age, employees who had a record of having recently undertaken an international mission were 0.89 times (95% CI 0.39 – 2.02) as likely to have filed a medical insurance claim relating to venous thrombosis as employees who had not recently undertaken such a mission.

The cases were identified using medical insurance claims. Eighty one cases of phlebitis, thrombophlebitis or thromboembolism (ICD-9 451 or 453) were identified (only the first claim for each employee was included), and 30 of these had deep vein thrombosis (ICD-9 451.1, 451.11, 451.19, 451.2, 453.9). To identify the flight-related events, the researchers identified all cases who filed an insurance claim after the beginning and within 30 days of completion of an international mission. Eleven cases with superficial or deep vein thrombosis were thus identified as being flight-related. It is not explained why the claim date was used instead of the date of diagnosis, but the researchers maintained that this was a reasonable approach because recent travellers with venous thrombosis appeared to file claims promptly and hence potential cases would not have been missed. Indeed the true number of cases could, according to the researchers, have been overestimated because it was not possible to examine personal medical files to verify the diagnosis. The controls (10 per case) were randomly selected from the records of insured employees who had not filed a claim for venous thrombosis before the date the case submitted his or her claim.

Although no association was found, the researchers rather surprisingly proposed that deep vein thrombosis should be regarded as a potential occupational hazard among

people frequently flying long distances for their work. However, it would be unwise to draw any conclusions from this study — the methods of case ascertainment were poor, the nominated index date was inappropriate, it is possible that exposure to long-distance air travel was incomplete (since only work-related travel was identified), and it was not possible to obtain information about possible confounders.

Arya et al (2002)

This study, which included 185 cases and 383 controls, was undertaken by researchers at King's College Hospital in London who concluded that travel was only associated with an increased risk of deep vein thrombosis in people with pre-existing risk factors (Arya et al. 2002). When the odds of deep vein thrombosis in travellers with at least one pre-existing risk factor was compared with the odds in non-travellers without risk factors, the unadjusted odds ratio for flights of more than eight hours in the four weeks before the diagnosis of deep vein thrombosis was 3.0 (95% CI 1.1 – 8.2). The corresponding estimate for travel of more than three hours by any mode of transport was 2.7 (95% CI 1.2 – 6.4). Conversely, when the presence or absence of risk factors was not taken into account, the unadjusted odds ratios were 1.2 (95% CI 0.6 – 2.3) for air travel of more than three hours, 1.3 (95% CI 0.6 – 2.8) for air travel of more than eight hours, and 1.4 (95% CI 0.7 – 2.6) for travel of more than three hours by any means.

However, the analysis was criticised by commentators who claimed that it was impossible to determine whether the elevated risk in people with pre-existing risk factors was attributable to travel or due to the risk factors themselves (Rosendaal et al. 2003b). The correct approach, they argued, was to restrict the analysis to cases and controls with at least one risk factor. The researchers undertook the recommended reanalysis and reported that the significantly elevated risk persisted for travel of more than three hours' duration by any form of transport (odds ratio 2.9 [95% CI 1.1 – 7.9]) (Arya and Cohen 2003). Among those with no additional risk factors, the odds ratio for any travel of more than three hours was 0.7 (95% CI 0.2 – 2.2). But inconsistencies in the number of controls reported to have risk factors raise questions about the reliability of these results. Of 31 controls who travelled, four of the 12 who were classified as having at least one pre-existing risk factor in the original paper were inexplicably reclassified as having no risk factors in the reanalysis.

As in the studies by Kraaijenhagen and colleagues (Kraaijenhagen et al. 2000; ten Wolde et al. 2003), the controls were patients initially suspected of having venous thrombosis, thus introducing the possibility of selection bias and an underestimation of any elevated risk. The researchers acknowledged that the media publicity about a perceived association between travel and venous thromboembolism might have resulted in a control series that was more similar to cases with respect to travel history than the population that gave rise to the cases. Moreover, it is impossible to ascertain from the information provided whether all of the eligible cases and controls participated in the study.

The researchers collected information about risk factors for venous thromboembolism such as a personal or family history of venous thromboembolism, obesity, hormonal therapies, pregnancy, immobilisation (undefined), malignancy, and surgery. It was found that a greater proportion of cases than controls had a personal history of venous thromboembolism (24.5% c.f. 15.7%) or had recently undergone surgery (12.5% c.f. 2.1%), and that 75.0% of the cases who travelled had at least one other risk factor for deep vein thrombosis, as compared with 38.7% of travelling controls. Although the researchers did stratify by the presence of risk factors, it is possible that the mix of those factors differed between cases and controls and hence residual confounding is possible. Moreover, neither sex nor age were accounted for in the analysis. This is relevant because a greater proportion of cases were male (49% c.f. 29%). Moreover, the age range observed among the 568 case and control patients was extremely wide (16 – 93 years). The range was not reported separately for cases and controls — instead, the researchers reported mean ages (cases 55 years, controls 54 years), which might have been skewed by extreme values. Finally, the researchers do not appear to have considered that some subjects, for example those who recently underwent surgery, may have been less likely to have travelled.

Hosoi et al (2002)

In this study undertaken at Ealing Hospital in London, which was based on 101 cases and 106 controls, the crude odds ratio for travel by air in the two weeks before the onset of symptoms was 0.8 (95% CI 0.3 – 1.9) (Hosoi et al. 2002). The estimate for travel by any mode of transport was 1.3 (95% CI 0.6 – 2.8). Unlike earlier case-control studies, all cases and controls who reported prolonged immobilisation (confined to a hospital,

nursing home or other chronic care facility) or surgery in two weeks before referral were excluded from the study as it was considered that these people would not have had the opportunity to undertake a recent journey.

There were significantly more travelling cases (73%) with thrombi confined to the popliteal or distal veins compared with non-travelling cases (37%), prompting the researchers to suggest that travel-related thrombi might have a preference for distal veins. However, it seems equally plausible that thrombi were simply diagnosed earlier in travellers, before they had time to propagate to more proximal veins.

Participants were identified using the same approach as the studies by Kraaijenhagen, Arya, and their colleagues (Kraaijenhagen et al. 2000; Arya et al. 2002; ten Wolde et al. 2003) — cases and controls were patients referred to the researchers' vascular unit with suspected deep vein thrombosis — and hence the study suffers from the same problems with potential selection bias. In fact, such bias could have been even more of an issue in this study because the cases were ascertained over a 15-month period between April 2000 and June 2001, whereas the controls were not selected until the final three months of the study (April 2001 to June 2001). Hence, the controls were obtained immediately after a period of intense media interest, especially in the UK, in the possible link between air travel and venous thromboembolism. The fact that a rather high proportion (11%) of controls had travelled by air in the two weeks before the onset of symptoms (all presented with leg pain and / or swelling) suggests that the prevalence of air travel in the population from which the cases was drawn may well have been overestimated. Ironically, the researchers themselves refer to the heightened media publicity, but do not appear to have considered the impact that this might have had on their study. Finally, in relation to the potential for selection bias, it is impossible to ascertain from the information provided whether all eligible cases and controls participated in the study.

All participants were asked about their medical history using a standardised questionnaire. This included enquiries about a personal or family history of venous thromboembolism, the use of hormone replacement therapy, known malignancy, pregnancy or post-partum status, trauma in the two weeks before referral, and age > 60 years. Surprisingly there is no indication that female patients were asked about oral contraceptive use. Cases with a history of travel were also examined to identify the

presence of any chronic venous insufficiency and obesity, and most of these cases also underwent thrombophilia screening. Although the researchers highlighted differences in the age distribution and the frequency of risk factors for deep vein thrombosis among the cases who travelled compared with those who did not, they do not appear to have considered the possibility of confounding.

Martinelli et al (2003)

In this study, which was undertaken at the Maggiore Hospital in Milan and included 210 cases and 210 controls, air travellers were twice as likely to develop non-fatal venous thromboembolism as non-travellers (Martinelli et al. 2003). The odds ratio for any air travel in the month before a venous thromboembolic event was 2.1 (95% CI 1.1 – 4.0); for flights of more than eight hours the estimate was 3.0 (95% CI 0.9 – 9.5). The researchers also observed an interaction between air travel and thrombophilia (factor V Leiden mutation, prothrombin G20210A, antithrombin deficiency, protein C or S deficiency, antiphospholipid antibodies, or homocysteinaemia). Compared with people who did not have thrombophilia and did not fly, the risk of non-fatal venous thromboembolism was 1.7 (95% CI 0.7 – 3.7) in air travellers without thrombophilia, 6.3 (95% CI 3.7 – 10.5) in non-travellers with thrombophilia, and 16.1 (95% CI 3.6 – 70.9) in air travellers with thrombophilia. Oral contraceptive use also modified the association between air travel and non-fatal venous thromboembolism. Compared with non-users who did not travel, the risk was 1.4 (95% CI 0.3 – 5.6) in air travellers who were non-users, 3.9 (95% CI 1.9 – 8.0) in users of oral contraceptive who did not fly, and 13.9 (95% CI 1.7 – 117.5) in oral contraceptive users who flew.

Cases were consecutive patients aged 20 – 70 years referred to a thrombosis centre between January 1999 and September 2001 for thrombophilia screening following a first diagnosis of proximal deep vein thrombosis or pulmonary embolism at some time in the previous 24 months. Patients with known malignancies were excluded from the study. No information was provided to allow a judgement as to whether the people with a recent history of venous thromboembolism who were referred to the centre had different characteristics from those who were not referred. For example, it has been suggested that this method of case ascertainment is likely to have introduced a bias because the cases would tend to be younger patients without other risk factors for venous thromboembolism (Watson 2005). However, it is also possible to argue that

such patients would be an ideal group to study because it is more likely that any increased risk in air travellers would be due to the travel exposure.

Controls were selected from a group of volunteers who had undergone thrombophilia testing during the study period. This group comprised friends or partners of all patients referred to the thrombosis centre. Volunteers were eligible for inclusion in the study if they had no personal history of venous thrombosis (determined using a validated questionnaire) or overt malignancy. One control, matched by age (10-year age bands), sex, and educational level, was selected for each case.

Participants were interviewed before their thrombophilia status was determined and were asked about the presence of transient risk factors for venous thromboembolism (including air travel, oral contraceptive use, hormone replacement therapy, pregnancy, surgery, trauma, and immobilisation) in the month before the index date. For cases, this was the date of the venous thromboembolic event, while for controls it was the date of their visit to the thrombosis centre. Because the cases did not visit the thrombosis centre immediately after the venous thromboembolic event (median 5 months, range 1 – 24 months), this raises the possibility of some differential recall about travel, oral contraceptive use, and the presence of potential confounders.

Sixty of 210 cases (28.6%) could not be tested for protein S or protein C deficiency because they were taking oral anticoagulants. Otherwise all cases and controls were screened, by independent blinded technicians, for the factor V Leiden and prothrombin G20210A mutations; antithrombin, protein C, protein S deficiencies; the presence of lupus anticoagulant and anticardiolipin antibodies: and plasma homocysteine levels. At least one thrombophilic abnormality was found in 102 (49%) cases and 26 (12%) controls. The most common abnormality was factor V Leiden mutation, which was present in 32 (15%) cases and six (3%) controls.

While the researchers employed individual-level matching, they appear to have undertaken an unmatched analysis (unexplained) in which they adjusted for only two (sex and age) of the three matching factors. If the level of education was associated with the likelihood of air travel, then the failure to adjust for this matching factor in the analysis might have led to an underestimate of the true association between air travel and venous

thromboembolism, since the matching would have made the controls more similar to the cases with respect to travel history than they would otherwise have been. The investigators adjusted for BMI, as well as sex and age, but made no mention of whether they had evaluated confounding by other factors. For example, several cases, but none of the controls, had transient risk factors for venous thromboembolism (such as surgery, trauma, immobilisation, pregnancy, and recently having given birth) which could also have reduced the likelihood of air travel. Failure to consider these factors in the analysis might have led to a further underestimation of the association between air travel and venous thromboembolism.

Cannegieter et al (2006)

In an ongoing population-based case-control study in the Netherlands, the Multiple Environmental and Genetic Assessment (MEGA) study, travel of more than four hours by any mode of transport in the two months before the index date carried a two-fold increase in risk (odds ratio 2.1 [95% CI 1.5 – 3.0]) (Cannegieter et al. 2006). No dose-response was found for duration of travel. The individual point estimates for travel by air (1.7 [95% CI 1.0 – 3.1]), car (2.2 [95% CI 1.3 – 3.7]), bus (2.2 [95% CI 0.8 – 6.3]), and train (3.5 [95% CI 0.8 – 16.8]) were all very similar. Because a review of the discharge letters and diagnostic reports of 742 cases revealed that the diagnosis of pulmonary embolism complied with the Dutch diagnostic standard in only 78% of patients, as compared with 97% of those with deep vein thrombosis, the researchers also undertook analyses confined to cases with deep vein thrombosis (and their controls). The odds ratio for air travel was larger (3.0 [95% CI 1.3 – 7.1]) than that found for travel by car, bus, or train (1.9 [95% CI 1.1 – 3.2]). Incidentally, these estimates are lower than those found in an earlier analysis (based on 829 cases and 829 controls) in which the investigators reported that travel by air was associated with six-fold increased risk of venous thromboembolism (odds ratio 5.8 [95% CI 2.0 – 16.6]), while those who travelled by other modes of transport had twice the risk of non-travellers (odds ratio 2.2 [95% CI 1.9 – 4.3]) (Rosendaal 2002).

In the later analysis, carriers of factor V Leiden who travelled by car, bus, or train had a six-fold increased risk of deep vein thrombosis when compared with non-travellers without the mutation (odds ratio 6.2 [95% CI 1.7 – 22.3]) (Cannegieter et al. 2006). For air travellers there was a corresponding 36-fold increase in risk (odds ratio 36.1 [95%

CI 3.8 – 344.1]). Conversely, there appeared to be no interaction between air travel and prothrombin G20210A. Multiplicative increases in risk were also observed for air travellers with a BMI > 30 kg/m² (odds ratio 7.1 [95% CI 2.0 – 24.9]) and height < 1.60 metres (odds ratio 6.8 [95% CI 1.1 – 43.5]) or > 1.90 metres (odds ratio 9.4 [95% CI 0.9 – 97.1]) when compared with non-travellers with a BMI < 25 kg/m² and a height between 1.60 and 1.90 metres respectively. Using a case-only approach (Khoury and Flanders 1996) to explore the possibility of an interaction between air travel and oral contraceptive use, it was estimated that women taking oral contraceptives who travelled by any means had a 15-fold increased risk of deep vein thrombosis when compared with non-users who did not travel. The corresponding increase for women who flew was 27-fold.

Cases were consecutive patients aged < 70 years who were referred to six regional anticoagulation clinics with a first episode of deep vein thrombosis or pulmonary embolism between March 1999 and May 2002. Patients who were unable to complete the questionnaire, those who died soon after the venous thromboembolic event, and persons in the terminal stages of a disease were excluded. Of the remaining 3,902 cases, 656 declined to participate or could not be traced and 135 were excluded because they were interviewed by telephone and no questions were asked about travel. Because the investigators chose to use the cases' spouses as their controls, this led to the exclusion of 687 cases because they were not married and another 557 because their spouse declined to participate – although 229 of the latter group were matched with the spouses of cases who were subsequently found to be ineligible. A further 190 cases were excluded because one or both members of the case/control pair gave information about travel *after* the index date. Hence, only 1,906 of 3,902 (48.8%) cases were included in the study.

For each case, their opposite sex spouse served as their control, except for the "spare" controls who were matched by sex and age to 229 of the 557 cases whose spouses did not want to participate. Thus, some case/control sets were opposite-sex pairs and others were same-sex. The investigators maintained that an advantage of choosing spouses as controls was that it provided some control for factors such as socio-economic status. Conversely, since spouses often travelled together, 135 case/controls pairs did not contribute to the matched analysis because their positive exposure status was concordant. This left 145 pairs in which either the case (*n=98*) or the control (*n=47*) had travelled.

The researchers reported that the risk of venous thromboembolism was greatest during the first week after a journey, however the only odds ratios which were provided related to an eight-week period following travel. It is likely, therefore, that these published odds ratios underestimated the true relative risks.

Both cases and controls completed a detailed questionnaire about risk factors for venous thromboembolism and were tested for factor V Leiden and prothrombin G20210A mutations. Although the researchers reported effect modification by factors such as factor V Leiden, BMI, and height, they didn't explore the possible role of confounding by other risk factors.

7.2.3 Case-crossover studies

A potential association between an exposure and outcome can be studied using a case-crossover design in situations where the exposure status changes over a short period of time, the outcome has a reasonably sudden onset with a short latency period, and the induction period is short (Maclure 1991). There are advantages to using such an approach to examine the potential association between air travel and venous thromboembolism — because each case serves as his or her own control and the required study period is short, confounding by inherent characteristics (for example, thrombophilia) and characteristics that are generally stable over short periods (for example, BMI) can be avoided. Moreover, characteristics that may change relatively quickly (for example, exposure to surgery, injury, immobility, pregnancy, and the use of oral contraceptives or hormone replacement therapy) can be adjusted for in the analysis if necessary. One disadvantage of the case-crossover approach is that any flight-related risk of venous thromboembolism might be modified by risk factors such as thrombophilia and hence it has been suggested that relative risks obtained from case-crossover studies should be generalised with caution (van der Bom 2003). Table 7.2 provides details of the case-crossover studies which have considered the risk of venous thromboembolism in travellers, following which each study is discussed in more depth.

Table 7.2 Case-crossover studies of travel and venous thromboembolism

Reference	Methods	Results	Comments
(Eekhoff et al. 2000)	Extension of Leiden Thrombophilia Study (LETS), but based solely on patients from Leiden (original study included 474 consecutive patients from anticoagulant clinics in Leiden, Amsterdam, and Rotterdam who had a first episode of objectively confirmed DVT and no known malignancy) because information about presence of minor risk factors before the onset of DVT had been recorded for these patients. Of 271 Leiden patients, 84 excluded because they had major acquired risk factors before onset of their DVT, hence 187 eligible patients. Follow-up questionnaire sent to 187 patients 4 years after inclusion in LETS study, enquired about the occurrence of minor events in the 2 weeks before receipt of questionnaire. Minor events defined as bed rest of > 12 hours a day for $\geq$ 2 consecutive days, heavy physical exertion, minor trauma, minor surgery, or prolonged (not defined) travel by car, bus or aeroplane. Further details of any events were obtained by telephone interview. 59/187 (31.6%) patients were excluded for various reasons (major medical events, pregnancy, declined to participate, could not be traced).	3-fold increased risk of DVT in people who had experienced minor events in preceding 2 weeks (RR 2.9 [95% CI 1.5 – 5.4]). Similar relative risk (2.4) when people with FVL mutation excluded. Estimated 17-fold increase in risk in people with minor events and FVL mutation compared with those without mutation and no minor events. Only 2/128 patients (1.6%) had travelled in the 2 weeks before the onset of their DVT compared with 5/128 (3.9%) in the later 2-week period.	The incidence of minor events (including travel) in the 2 weeks before the DVT might have been underestimated for two reasons: (i) The LETS questionnaire did not include specific questions about minor events. Instead this information was spontaneously recorded by the investigators. (ii) The subjects who could be traced and were willing to complete the follow-up questionnaire might have been more likely to travel than those who were not followed up.

Reference	Methods	Results	Comments
(Kelman et al. 2003) (Original analysis) (Becker et al. 2006) (Reanalysis)	***Original analysis*** Identified all admissions (16,205 admissions, 13,184 patients) to Western Australian hospitals between 1981 and 1999 for which the principal discharge diagnosis was DVT or PE. Estimated sex and age-specific incidence rates for first episode of VTE. Australian migration data linked to hospital records to identify all individuals of any age who had undertaken at least one international flight and been admitted to a Western Australian hospital with VTE between 1981 and 1999 (2,279 Australian and 3,129 non-Australian citizens). Identified subset admitted ≤ 100 days of arrival (153 Australian and 438 non-Australian citizens) and estimated expected number of events within defined periods following international flight (assuming a uniform distribution during 100 days following flight). Compared incidence rate of VTE for Australian citizens within defined time periods following international flight with background risk (≤ 100 days after flight). ***Reanalysis*** Allowed for ageing during study period, excluded time spent outside Australia, included non-Australian citizens.	***Original analysis*** Observed number of cases in 14 days after international flight was greater than expected, assuming uniform distribution of cases during 100 days following flight (46 c.f. 22.1 for Australian citizens and 200 c.f. 63.2 for non-Australians). "Healthy traveller" effect for Australian citizens, observed number of cases less than expected based on estimated population sex and age-specific rates (46 c.f. 102.7). Opposite true for non-Australians (200 c.f. 105.3). Risk of VTE admission following international flight compared with baseline: 4.17 (95% CI 2.94 – 5.40) in first 2 weeks 5.61 (95% CI 3.94 – 7.97) in first week 2.63 (95% CI 1.55 – 4.45) in second week No increased risk in third week. Absolute risk of VTE in Australian citizens who undertook international flight lower than risk in non-Australians (9.6 c.f. 43.5 per million arrivals). Risks attributable to international flights: 7.3 and 33 per million arrivals for Australian and non-Australian citizens respectively. Estimated rate of death from flight-related VTE: 0.5 per million arrivals. ***Reanalysis*** Relative risk of VTE following an international flight same in Australian and non-Australian citizens. Relative risk of VTE being triggered following international flight compared with baseline: 29.8 (95% CI 22.4 – 37.3) on day of flight 3.84 and 1.94 (95% CIs not given) for first and second weeks respectively.	***Original analysis*** 1. Expected number of admissions of non-Australian citizens in the 2 weeks following a flight probably: (i) *Underestimated* when based on number of admissions during 100 days following flight. (ii) Probably *overestimated* when based on Australian population sex and age-specific rates. 2. Non-Australian citizens excluded from analyses to calculate relative risk. 3. Assumed that time spent away from Western Australia was negligible. 4. Not possible to examine effect of flight duration. 5. Did not allow for ageing over study period. 6. Possible that some patients were included in the denominator but not numerator, for example: deaths outside hospital, international arrivals whose intended destination was Western Australia but admitted to hospital immediately on arrival at an international airport in another state, and DVT events treated as an outpatient.

Abbreviations used in the table DVT: deep vein thrombosis, FVL: factor V Leiden, PE: pulmonary embolism, RR: relative risk, VTE: venous thromboembolism.

Eekhoff et al (2000)

This extension of the Leiden Thrombophilia Study employed a case-cross over analysis to explore the association between minor events and deep vein thrombosis (Eekhoff et al. 2000). The proportion of cases who suffered from minor events was compared during two periods: the two weeks before the onset of the first episode of deep vein thrombosis and the two weeks preceding the receipt of a follow-up questionnaire which was sent to the participants four years later. The occurrence of minor events was associated with a three-fold increased risk of a first episode of deep vein thrombosis (odds ratio 2.9 [95%CI 1.5 – 5.4]). Only 2/128 patients (1.6%) had a recorded history of travel in the two weeks before the onset of their deep vein thrombosis, compared with 5/128 (3.9%) who reported travel in the later two-week period, but it is possible that the incidence of travel in the initial period was underestimated because the information was not obtained systematically. It is also possible that the people who agreed to complete the follow-up questionnaire were different with respect to the likelihood of travel during the later period than those who did not wish to participate or could not be traced (one third of the eligible group).

Kelman et al 2003

In this study, which linked national immigration data with Western Australian hospital admissions data, the incidence rate of venous thromboembolism in Australian citizens in the first week following an international flight was almost six times the baseline rate (relative risk 5.61 [95% CI 3.94 – 7.97]) (Kelman et al. 2003). The relative risk was 2.63 (95% CI 1.55 – 4.45) in the second week after an international flight and was not significantly elevated in the third week. The overall risk of venous thromboembolism in the first two weeks after a long-distance flight was 4.17 (95% CI 2.94 – 5.40). Sex and age did not modify the risk. Because of uncertainties about the size of the denominator with increasing time since arrival, cases who were not Australian citizens were not included in these analyses.

In the first 14 days after an international flight, the number of observed cases exceeded the number expected for both Australian (46 c.f. 22.1) and non-Australian citizens (200 c.f. 63.2). The expected number of cases was obtained by counting the number of cases which occurred within 100 days following an international flight and then calculating the number that would be expected during a two-week period assuming a uniform

distribution throughout the 100-day period. However, the researchers cautioned that the expected number of non-Australian cases was probably underestimated because many visitors remained in Western Australia for less than 100 days and therefore some cases of venous thromboembolism would have been missed.

A "healthy traveller" effect was observed among the Australian citizens; the observed number of cases in the two weeks following a flight (*n=46*) was substantially lower than the number expected (*n=102.7*) based on Western Australian population rates. The opposite was found for non-Australian citizens, although it was thought that the expected number of cases had been overestimated because this figure was obtained by applying the sex and age-specific rates of venous thromboembolism to the number of arrivals by non-Australian citizens and assuming that such visitors remained in Western Australia for 100 days.

The estimated absolute risks also differed between Australian and non-Australian citizens; the overall rates were 9.6 and 43.5 cases per million arrivals respectively and the cases attributable to an international flight were 7.3 and 33 per million arrivals. The researchers found that the higher risk in non-Australians was not due to differences in the sex and age distribution, and suggested that it might be due to differences in flight duration, differences in underlying risk, or different thresholds for hospital admission when compared with Australian citizens. Unfortunately it was not possible to examine the effect of flight duration using the existing data.

It was estimated that the annual risk of venous thromboembolism would be increased by 12% in persons undertaking one international flight per year. Based on five inpatient deaths and 9.4 million arrivals of all ages during the study period, the estimated absolute risk of fatal events was 0.5 deaths per million arrivals. This is likely to be an underestimate of the total population rate, since deaths which did not occur in hospital were excluded. Moreover it should be remembered that discharge diagnoses are coded differently from causes of death — discharges are coded to the principal reason for admission, while deaths are coded to the underlying cause. Hence, patients who had recently undergone surgery or who had disseminated cancer, for example, would have been included in this study if they survived the venous thromboembolic event. On the

other hand, they should have been excluded if they died in hospital from pulmonary embolism.

In a later analysis, the researchers removed person-years not spent in Australia and accounted for ageing over the study period (Becker et al. 2006). The relative risks of flight-related venous thromboembolism in Australian citizens and the non-Australian citizens were not significantly different in this analysis. Moreover, since many of the non-Australian citizens were found to be long-term residents of Australia, their exclusion from the original analysis was judged to have been unnecessary. This allowed the pooling of data from both groups (and a consequent increase in power) to estimate the risk of venous thromboembolism following an international flight relative to the baseline risk. The risk for all ages of a venous thromboembolic event being triggered on a day on which an international flight was undertaken was 30 times higher than the risk on a non-flying day (relative risk 29.8 [95% CI 22.4 – 37.3]). Although this is a large relative risk, the researchers stressed that for most people the baseline probability that a venous thromboembolic event would be triggered on a single day was very small and hence the absolute risk of a venous thromboembolic event being precipitated on the day of a flight was also small. When slightly longer periods were considered, it was found that the relative risks of being admitted to hospital with venous thromboembolism in the first and second weeks following an international flight were 3.84 and 1.94 respectively (95% CI not provided). These estimates were said to be lower than those obtained in the earlier analysis because ageing during the study period was now accounted for and person-years spent away from Australia were now excluded rather than ignored. Sex did not modify the risk, but the researchers pointed to weak evidence that the relative risk increased slightly with age.

7.2.4 Cohort studies

Only one cohort study has estimated the relative risk of venous thromboembolism associated with air travel (Schwarz et al. 2003). The details of this study are shown in Table 7.3.

Table 7.3 Cohort study of travel and venous thromboembolism

Reference	Exposed	Unexposed	Information sought	Outcomes	Relative risk (95% CI)	Comments
(Schwarz et al. 2003)	Enrolled 1081 persons who intended to undertake long-distance air travel (non-stop outbound and return flights ≥ 8 hours). Recruited through advertisements in travel agencies, local newspapers, and on radio and television. Exclusion criteria: < 18 years, life expectancy < 3 months, venous thrombosis on baseline US, any use of compression stockings/bandages or anticoagulants. 4 had thrombosis at baseline and 113/1077 (10.5%) excluded from final analysis (22 [2.0%] declined follow-up examination, 87 [8.1%] used compression stockings/bandages or anticoagulants in association with air travel, 4 [0.4%] treated with anticoagulants for reasons other than venous thrombosis). 964 included in final analyses.	Enrolled 1230 persons who did not intend to undertake long-distance air travel within 3 months of entry into study. Recruited using same methods as for exposed group. Exclusion criteria: as for exposed, although unclear whether users of compression stockings/bandages also excluded. 1 had thrombosis at baseline and 16/1229 (1.3%) excluded from final analysis (9 [0.7%] declined follow-up examination, 7 [0.6%] treated with anticoagulants for reasons other than venous thrombosis). 1213 included in final analyses.	At baseline Risk factors for VTE, coagulation and thrombophilia screening, D-dimer, compression and Doppler US (1 week before outbound flight for exposed group). Standardised US protocol Each examination undertaken independently by 2 physicians blinded to exposure status. Confirmation of PE V-Q scan. Follow-up Any new risk factors for VTE, any symptoms, D-dimer, US (48 hours after return flight in exposed, mean of 25 days after baseline visit in unexposed). Repeat US and telephone interview 4 weeks after 1st follow-up visit (exposed and unexposed).	Isolated calf muscle venous thrombosis 20/964 exposed, 10/1213 unexposed. DVT 7/964 exposed, 2/1213 unexposed. Symptomatic PE 1/964 exposed (passenger with US evidence of DVT) No deaths. All events diagnosed at 1st follow-up visit. All participants attended for 2nd follow-up, no further events.	**Unadjusted RR** Flight > 8 hours, isolated calf muscle venous thrombosis 2.52 (1.20 – 5.26) Flight > 8 hours, DVT 4.40 (1.04 – 18.62) Flight > 8 hours, venous thrombosis (isolated calf muscle and DVT combined) 2.83 (1.46 – 5.49)	1. Clinical relevance of events unclear. 2. Shorter mean follow-up time for unexposed, possible underestimation of incidence (cumulative) in unexposed. 3. Biases towards *overestimation* of incidence of venous thrombosis in air travellers (because volunteers) and *underestimation* because: (i) Excluded users of compression stockings, bandages, and anticoagulants possibly at higher background risk. (ii) Other in-flight preventive measures. (iii) Extension of isolated calf muscle venous thrombosis to DVT possibly prevented by treatment with heparin. 4. Did not address potential confounding.

Abbreviations used in the table DVT: deep vein thrombosis, PE: pulmonary embolism, US: ultrasound, V-Q scan: ventilation-perfusion scan, VTE: venous thromboembolism.

Schwarz et al. 2003

In this study, based on 964 passengers who departed from and returned to Germany on flights of at least eight hours' duration and a concurrent comparison group of 1213 non-travellers, the crude relative risks of deep vein thrombosis and of isolated calf muscle (soleus or gastrocnemius) venous thrombosis were 4.4 (95% CI 1.04 – 18.62) and 2.52 (95% CI 1.20 – 5.26) respectively. The relative risk for both types of event combined was 2.83 (95% CI 1.46 – 5.49).

A major limitation of this study is that the clinical relevance of the venous thrombotic endpoints is uncertain. First, most events were asymptomatic and were diagnosed by compression ultrasound, which was undertaken on each participant both before and after the exposure period by two physicians who were blinded to exposure status. Of the participants diagnosed with deep vein thrombosis, 5/7 air travellers and 1/2 non-travellers had no symptoms. Of those with isolated calf muscle venous thrombosis, 19/20 air travellers and 10/10 non-travellers were asymptomatic. Second, elevated D-dimer levels were found in only 4/7 air travellers and 1/2 non-travellers diagnosed with deep vein thrombosis and 7/20 air travellers and 2/10 non-travellers with isolated calf muscle venous thrombosis. As discussed in Chapter 1, normal D-dimer levels in the context of a low pre-test probability have a high negative predictive value (Blann and Lip 2006). Third, although the researchers conceded that little is known about the natural history of isolated calf muscle venous thrombosis, this was the primary outcome that the study was powered to detect. Information from a pilot study was used to calculate the required sample size (Schwarz et al. 2002). In justifying their choice of primary outcome, the researchers referred to a study which suggested that isolated thrombosis in the veins of the soleus and gastrocnemius muscles was "the first step toward DVT" (Masuda et al. 1998). The researchers then went on to conclude that the incidence of isolated calf muscle venous thrombosis "may be used as a surrogate marker of DVT associated with air travel". This conclusion was criticised by a member of another research group which had followed 135 patients who were initially suspected of having deep vein thrombosis, but were found on ultrasound to have isolated calf muscle vein thrombosis (Kahn 2004). All of the 135 patients had symptoms, but only 3% had ultrasonic evidence that the thrombus had extended to the popliteal vein during the three-month follow-up period (MacDonald et al. 2003).

A second concern is that the mean follow-up period for non-travellers was significantly shorter than that for air travellers. Hence, it is possible that the cumulative incidence of venous thrombotic events in non-travellers was underestimated and the relative risk overestimated.

A third limitation of the study is that it was based on volunteers who are likely to have had a particular interest in taking part in the study and may have had a higher baseline risk than the general population. Hence, it is possible that the cumulative incidence of venous thrombosis in air travellers was overestimated. However the inclusion of people at higher baseline risk is unlikely to have over-inflated the relative risk because most pre-existing risk factors for venous thromboembolism were equally distributed between air travellers and non-travellers.

It is possible, however, that the relative risk was biased downwards because 87 (8.1%) air travellers initially enrolled in the study were excluded from the final analysis because they used prophylactic heparin or compression stockings. If these people were at higher baseline risk than the other air travellers, then their exclusion could have deflated the true relative risk. The researchers identified two other factors which could have led to an under-estimation of the relative risk. First, the air travellers were encouraged to drink plenty of non-alcoholic fluids, perform stretching exercises, and to walk about the cabin during their flights — although it is not known whether the participants complied with these suggestions, or indeed, whether these measures reduce the risk of venous thromboembolism. Second, participants with isolated calf muscle vein thrombosis were all diagnosed 48 hours after their flight and were given a 10-day course of low-molecular weight heparin. According to an earlier study by the researchers, such a regimen prevents thrombus progression (Schwarz et al. 2001).

Finally, the researchers made no mention of exploring possible confounding despite acknowledging that there were more women, and more people with varicose veins and venous insufficiency, in the non-travelling group. Moreover, among those who developed deep vein thrombosis, the air travellers were younger than the non-travellers.

7.2.5 Intervention studies

It is not surprising that no prospective studies have explored the association between air travel and symptomatic, clinically relevant, venous thromboembolism. One commentator has estimated that, assuming a background incidence of venous thromboembolism of two cases per 1,000 person-years, 80% power, and alpha of 0.05, a sample size of 100,000 exposed and 100,000 unexposed would be required to detect a four-fold increase in risk in the two weeks following a long-distance flight (MacGillavry et al. 2001). Such a study would clearly be expensive and logistically difficult. Moreover, the practical and ethical constraints of randomly allocating people to undertake long-distance flights mean that it is highly unlikely that an intervention study will ever be undertaken to examine the association between air travel and venous thromboembolism. There have, however, been several randomised controlled trials of interventions designed to prevent flight-related venous thromboembolism. These studies will be discussed briefly later in the chapter.

7.2.6 Discussion

To return to the question posed at the beginning of this chapter, overall, the evidence from epidemiological studies is consistent with an association between air travel and venous thromboembolism, although that risk is poorly defined. Eleven analytical epidemiological studies have examined the potential association between travel and venous thromboembolism: eight case-control studies, two case-crossover analyses, and one cohort study. However, as has been shown in the preceding sections, the quality of most of these studies is poor and thus no attempt has been made in this chapter to perform a meta-analysis. The most reliable relative risk estimates suggest that compared with non-travellers, air travellers have in the order of a four-fold increased risk of developing non-fatal venous thromboembolism in the week following a long-distance flight. On the day of a flight, the risk that a venous thromboembolic event will be triggered increases by about 30-fold relative to the background incidence. The relative risk of fatal events has not been examined.

At this point it is useful to reflect on Bradford Hill's suggested criteria for assessing the likelihood of a causal relationship (Bradford Hill 1965): the strength of the association is not inconsequential; the association has been observed in different populations and in case-control and case-crossover studies; although it is impossible to be certain about the

timing of the pathological onset of venous thromboembolism, it appears that the travel exposure preceded the onset of symptoms; as already mentioned, there is evidence of a dose-response relationship between the duration of air travel and the incidence of pulmonary embolism; and, as will be discussed in a later section, it is biologically plausible that remaining seated for prolonged periods in cramped conditions might lead to venous thrombosis. In light of these considerations, there appears to be sufficient grounds for accepting that the relationship between long-distance air travel and venous thromboembolism is likely to be causal. Hence, it is appropriate to proceed to a consideration of the subsidiary questions posed in the introduction to this chapter.

7.3 DO OTHER RISK FACTORS MODIFY THE RISK OF FLIGHT-RELATED VENOUS THROMBOEMBOLISM?

As discussed earlier, several researchers have reported an interaction between air travel and oral contraceptive use (Martinelli et al. 2003; Cannegieter et al. 2006), thrombophilia (Martinelli et al. 2003; Cannegieter et al. 2006), BMI > 30 kg/m^2 (Cannegieter et al. 2006), height < 1.60 metres (Cannegieter et al. 2006), height > 1.90m (Cannegieter et al. 2006), and other risk factors for venous thromboembolism (Arya and Cohen 2003). An interaction between temporary risk factors for deep vein thrombosis, including travel, and the factor V Leiden mutation has also been reported (Eekhoff et al. 2000).

Two other studies have been undertaken with the express purpose of determining whether certain groups of air travellers are more likely to develop venous thromboembolism than others (Jacobson et al. 2003; Paganin et al. 2003). Details of these studies can be found in Table 7.4 and this is followed by a discussion.

Table 7.4 Additional studies which attempted to identify whether certain groups of air travellers are at particular risk of venous thromboembolism

Reference	Study design	Participants	Information sought	Results	Comments
(Jacobson et al. 2003)	Cohort	"Low and intermediate risk" passengers on 11-hour flights between London and Johannesburg. Exclusion criteria: previous VTE, anticoagulant use, pregnancy, recent surgery, intention to use compression stockings on flight, raised D-dimer levels before flight (9/491 assayed). 180 recruited in business class (33.9% female, median age 47 years [range 28 – 78]) and 719 in economy class (48.8% female, median age 43 years [range 18 – 81]).	D-dimer at check-in. D-dimer, thrombophilia screening, duplex US on arrival in Johannesburg. Telephone enquiry after 6 months about any symptoms or diagnoses of VTE.	On arrival 0/434 had DVT on US, 74/899 had raised D-dimer levels. OR (95% CI) for raised D-dimer levels after flight FVL 3.36 (1.17 – 9.63) Aspirin use 2.04 (1.04 – 3.99) HRT 2.15 (0.91 – 5.10) OC 1.23 (0.42 – 3.62) After 6 months 0/505 had been diagnosed with VTE.	1. Participation rates for each class of travel not stated. 2. Insufficient power to compare incidence by class of travel. 3. Batch of pre-flight D-dimer results available for only 54% of passengers. 4. Incomplete follow-up. 5. Potential confounding not explored.
(Paganin et al. 2003)	Case-control	Cases: 46 people diagnosed with DVT (US) or PE (spiral CT scan, angiography, or V-Q scan) during 1997 who had undertaken 11-hour flight from Paris to Réunion Island < 15 days before onset of symptoms. Ascertained through all 750 doctors on Island "who might be expected to treat VTE." Controls: On 4 days during 1997, questionnaire provided to 25 passengers disembarking from a flight from Paris. 92 passengers who remained symptom-free 15 days after flight were included.	Cases and controls completed questionnaire which enquired about class of travel, aisle or non-aisle seat, in-flight behaviour (alcohol, hypnotics, number of times that left seat), medication to prevent thrombosis, pre-existing risk factors for VTE.	OR (95% CI) for VTE Past VTE 63.3 (3.6 – 1098) Obesity 9.6 (2.9 – 31.5) Varicose veins 10.0 (3.7 – 27.0) Cardiac disease 8.9 (1.0 – 82.0) Recent injury 13.6 (1.5 – 117) Failure to leave seat 9.3 (2.5 – 35.0) No significant risk was found for "oestrogen treatment", travel in economy class, non-aisle seat, alcohol consumption in-flight, or the use of hypnotics.	1. Did not include cases who died before reaching hospital. 2. Participation rates of eligible cases and controls not stated. 3. Not stated whether controls randomly selected. 4. Possible recall bias. 5. Potential confounding not explored.

Abbreviations used in the table CT: computed tomography, DVT: deep vein thrombosis, FVL: factor V Leiden, HRT: hormone replacement therapy, OC: oral contraceptive use, OR: odds ratio, US: ultrasound, V-Q scan: ventilation-perfusion scan, VTE: venous thromboembolism.

Jacobson et al (2003)

One of the aims of this cohort study was to compare the incidence of venous thromboembolism in business class passengers who undertook an 11-hour non-stop flight from London to Johannesburg with the incidence in those who travelled in economy class (Jacobson et al. 2003). Unfortunately, insufficient volunteers were recruited in the former group to allow this comparison. In fact it is unclear how many potential participants, who were approached as they checked in for their flights on a South African airline, agreed to take part in the study. Moreover, while all 899 participants had a D-dimer test directly after their flight, only 434 agreed to undergo an ultrasound examination at the Johannesburg International Airport (*n=328*) or at a local hospital within one week of landing (*n=47*). Seventy-four passengers had raised D-dimer levels after their flight, but only 38 of these had an ultrasound. None of these 38 passengers, or any of the other travellers who were examined ultrasonically, had ultrasonic evidence of venous thrombosis. Telephone contact was made with 505 participants (including 64/74 passengers with elevated D-dimers) six months later and none reported signs or symptoms of venous thromboembolism following the index flight. One man did, however, develop symptomatic deep vein thrombosis after his sixth subsequent long-distance flight. It should be noted that, due to a technical problem, the results of pre-flight D-dimer assays were available for only 482 of the 899 participants. Hence, it is possible that some of the passengers with positive tests on arrival might also have had raised levels before they flew.

Further aims of the study were to explore the risk of venous thromboembolism in travellers with pre-existing risk factors and to evaluate in-flight behaviours. In unadjusted analyses, the researchers reported a positive association between the factor V Leiden mutation and raised D-dimer levels (odds ratio 3.36 [95% CI 1.17 – 9.63]) and a borderline significant result for aspirin use (odds ratio 2.04 [95% CI 1.04 – 3.99]). Possible explanations suggested for the latter result were that aspirin was taken by people at higher risk of venous thromboembolism or alternatively aspirin users had developed gastritis and hence had falsely raised D-dimer levels. No significant associations were noted for other thrombophilic mutations, smoking, weight, height, age, sex, or the use of other non-steroidal anti-inflammatory drugs, hypnotics, oral contraceptives, or hormone replacement therapy. Interestingly, despite participating in a study of flight-related venous thromboembolism, there was no evidence that passengers in either class had increased their fluid intake, limited the consumption of

alcohol, or performed the exercises recommended in the in-flight magazine. Indeed only 6% of all passengers in both classes exercised during their flight.

Paganin et al (2003)

This population-based case-control study was undertaken by researchers on Réunion Island, in the Indian Ocean, to ascertain risk factors for developing venous thromboembolism among people who had been on an 11-hour flight from Paris (Paganin et al. 2003). Passengers were more likely to develop venous thromboembolism if they had a history of previous events (odds ratio 63.3 [95% CI 3.6 – 1098]), were obese (odds ratio 9.6 [95% CI 2.9 – 31.5]), had varicose veins (odds ratio 10.0 [95% CI 3.7 – 27.0]), had cardiac disease (odds ratio 8.9 [95% CI 1.0 – 82.0]), had suffered a recent injury (odds ratio 13.6 [95% CI 1.5 – 117]), or if they had not left their seat during the flight (odds ratio 9.3 (95% CI 2.5 – 35.0). All odds ratios appear to have been unadjusted. No significant risk was found for "oestrogen treatment", travel in economy class, sitting in a non-aisle seat, consumption of alcohol, or the use of hypnotics.

The methods of this study were not clearly described, but it is possible that not all cases were ascertained — the investigators stated that they had no way of determining the true number of cases because venous thromboembolic events were not notifiable to health authorities. Moreover, pathologists were not included on the list of medical staff that the investigators approached to identify cases, so presumably cases who died suddenly in the community were excluded. Indeed, at least two such potential cases were excluded — these passengers, who died on arrival, were said to have symptoms highly suggestive of pulmonary embolism, but no definitive diagnosis was available.

On four occasions during the study period, 25 passengers arriving from Paris were selected as controls and were given the same questionnaire as the cases. The researchers did not explain how these people were chosen, and given that the exposures of interest in this study were risk factors for venous thromboembolism and in-flight behaviours, any failure to obtain a random sample could have resulted in a bias. For example, if the first 25 passengers to disembark were selected, it is likely that they were generally healthier and more mobile than those who disembarked later and hence the risk associated with particular characteristics could have been overestimated. Ninety-two of the controls who received a questionnaire returned it, but it is not stated whether

the questionnaire was accepted by all of the potential controls who were approached. It is also unclear when exactly the controls completed the questionnaire — although they received the questionnaire on arrival, it appears that they were required to wait for two weeks before returning it to ensure that they had not developed symptoms of venous thromboembolism. However this would not have prevented them from answering the questions about in-flight behaviour immediately, introducing the possibility of a recall bias since cases were asked the same questions up to 15 days later. It is likely that factors such as the number of times an individual left their seat during the flight would be recalled more accurately immediately after the flight. Interestingly, the only behaviours that differed between cases and controls were the average number of times they left their seats and the proportions in each group who did not leave their seats at all during the flight.

The final limitation of the study is that the researchers gave no indication that they had explored potential confounding.

7.4 WHAT IS THE ABSOLUTE RISK OF VENOUS THROMBOEMBOLISM IN LONG-DISTANCE AIR TRAVELLERS?

7.4.1 Incidence studies

Incidence studies of symptomatic venous thromboembolism have nearly all involved non-fatal events in passengers requiring medical care on arrival at international airports as shown in Table 7.5. A dose-response relationship between flight duration and the absolute risk of pulmonary embolism was observed in two of these studies (Lapostolle et al. 2001; Perez-Rodriguez et al. 2003). Rates per million arrivals at Charles de Gaulle Airport were 0.11 (95% CI 0.01 – 0.71), 0.40 (95% CI 0.19 – 0.79), 2.66 (95% CI 1.83 – 3.79), 4.77 (95% CI 2.66 – 8.41) for flights of 3 – 5 hours, 6 – 8 hours, 9 – 11 hours, and 12 or more hours respectively (Lapostolle et al. 2001). Rates of similar magnitude were observed among arrivals at Charles de Gaulle and Orly (Clerel and Caillard 1999), Madrid-Barajas (Perez-Rodriguez et al. 2003) and Sydney (Hertzberg et al. 2003) airports. These studies are likely to have underestimated the true incidence of venous thromboembolism among air travellers, since those who died from pulmonary embolism during a flight or on arrival were excluded, as were those who developed deep vein thrombosis or became symptomatic after leaving the airport.

Two of the studies outlined in Table 7.5 did include people who developed symptoms of venous thromboembolism, including deep vein thrombosis, after leaving the airport (Kelman et al. 2003; Paganin et al. 2003). In the Western Australian record-linkage case-crossover study, the incidence of venous thromboembolism in the two weeks following an international flight was 9.6 per million arrivals for Australian citizens (Kelman et al. 2003). Conversely, the absolute risk in the two weeks following an 11-hour flight to Réunion Island was an order of magnitude higher (116 cases per million arrivals) (Paganin et al. 2003). It is unclear why the latter figure is so much higher than the first since it was reportedly based on objectively confirmed deep vein thrombosis and pulmonary embolism. Moreover, many passengers arriving in Western Australia would have undertaken equally long journeys.

There is very little information about pulmonary embolism mortality in air travellers. In one study, the rate was reported to be less than one per million arrivals, although it was not possible to calculate a precise incidence from the available data (Kline et al. 2002). A rate of 7.6 deaths per million arrivals on flights of 11 hours can be derived from data presented by the Réunion Island researchers (Paganin et al. 2003), although this estimate excludes people who died from pulmonary embolism before reaching hospital. The only study to explicitly estimate the incidence of fatal events was the Western Australian study which also excluded people who died in the community (Kelman et al. 2003). The risk of dying from pulmonary embolism following an international flight was estimated to be 0.5 per million arrivals.

Table 7.5 Incidence of symptomatic venous thromboembolism in air travellers

Reference	Observation period	VTE events in arriving passengers	Number of arrivals (millions)	Absolute risk per million arrivals (95% CI)
(Clerel and Caillard 1999)	1998	15 cases of PE seen at the medical department at Aeroports de Paris on arrival at Charles de Gaulle or Orly airports, Paris. Median duration of travel 12 hours (range 3 – 15).	3	Risk of PE 0.5
(Lapostolle et al. 2001)	Nov 1993 – Dec 2000	56 cases of confirmed PE who required medical care and transfer to hospital on arrival at Charles de Gaulle Airport, Paris, after flights of 3 – 5 hours (1), 6 – 8 hours (9), 9 – 11 hours (33), ≥ 12 hours (13).	By duration of air travel < 3 hours: 88.49 3 – 5 hours: 9.18 6 – 8 hours: 22.53 9 – 11 hours: 12.37 ≥ 12 hours: 2.72 Total arrivals: 135.29	Risk of PE by duration of air travel < 3 hours: 0 (0.0 – 0.04) 3 – 5 hours: 0.11 (0.01 – 0.71) 6 – 8 hours: 0.40 (0.19 – 0.79) 9 – 11 hours: 2.66 (1.83 – 3.79) ≥ 12 hours: 4.77 (2.66 – 8.41) Overall risk: 0.4
(Kline et al. 2002)	Jan 1992 – June 2001	No deaths from PE in passengers who required medical care and transfer to hospital on arrival at Charlotte-Douglas Airport, North Carolina, after a trans-Atlantic flight. Also no flight-related deaths found in review of records of people who died from PE in the community.	Trans-Atlantic flights 1.1	Risk of fatal PE immediately after trans-Atlantic flight < 1.0
(Hertzberg et al. 2003)	Jan 1998 – Jan 2001	17 cases of confirmed PE who required medical care and transfer to hospital on arrival at Sydney Airport. All had flown ≥ 9 hours.	Air travel > 9 hours 6.58	Risk of PE with air travel > 9 hours 2.57
(Kelman et al. 2003)	1981 – 1999	46 Australian citizens with confirmed DVT or PE who were admitted to Western Australian hospitals within 2 weeks of an international flight.	International flight 4.8	Risk of VTE 9.6

Reference	Observation period	VTE events in arriving passengers	Number of arrivals (millions)	Absolute risk per million arrivals (95% CI)
(Perez-Rodriguez et al. 2003)	Jan 1995 – Dec 2000	16 cases of confirmed PE who required medical care and transfer to hospital on arrival at Madrid-Barajas Airport after flights of 6 – 8 hours (1), > 8 hours (15).	By duration of air travel < 6 hours: 28.0 6 – 8 hours: 3.9 > 8 hours: 9.1 Total arrivals: 41.0	Risk of PE by duration of air travel 6 – 8 hours: 0.25 (0.0 – 0 .75) > 8 hours: 1.65 (0.81 – 2.49) Overall risk: 0.39 (0.20 – 0.58)
(Paganin et al. 2003)	1997	46 cases of confirmed VTE (33 DVT only, 13 PE) who received medical care within 2 weeks of 11-hour flight.	Air travel 11 hours 0.4	Overall risk of DVT and PE with air travel 11 hours 116 Risk of fatal PE with air travel 11 hours 7.6

Abbreviations used in the table DVT: deep vein thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism.

7.4.2 Other sources of information about absolute risk

High rates of asymptomatic and symptomatic venous thrombosis have been reported in studies of volunteers who undertook long-distance air travel (Table 7.6). As discussed in the introduction to this chapter, the finding that 10% of controls in a randomised controlled trial of graduated compression stockings had ultrasonic evidence of asymptomatic distal deep vein thrombosis following a long-distance flight received extensive media coverage (Scurr et al. 2001). However the validity and clinical relevance of this finding was questioned in an accompanying editorial (Hirsh and O'Donnell 2001). The commentators' concerns were that the interpretation of calf vein ultrasonography is a subjective process and that there was no assurance that the technicians had remained blinded to treatment group. In addition, none of the controls who were diagnosed with thrombosis had symptoms and only half had elevated D-dimer levels. This suggested, according to the commentators, that either the thrombi were very small or the ultrasound results were falsely positive. The other studies in which asymptomatic venous thrombosis was detected had similar limitations (Arfvidsson et al. 1999; Belcaro et al. 2001; Belcaro et al. 2002; Cesarone et al. 2002; Belcaro et al. 2003; Jacobson et al. 2003; Schwarz et al. 2003; Cesarone et al. 2003a; Cesarone et al. 2003b; Cesarone et al. 2003c; Cesarone et al. 2003d; Belcaro et al. 2004).

In only one of the studies involving volunteers were most cases symptomatic (Hughes et al. 2003). In this uncontrolled cohort study, 1.0% (95% CI 0.5 – 1.9) of participants had radiological evidence of venous thromboembolism in the three months following outbound and return flights of at least four hours' duration, although the exact timing of the diagnoses is not stated. Interestingly, almost identical proportions of volunteers had raised D-dimer levels before travel (these were excluded from the study) and within 72 hours of their return; the proportions were 8.3% (83/1,000) and 8.7% (76/878) respectively. The numbers of cases of venous thromboembolism within each of these groups were not stated, however if similar proportions had radiological signs of venous thromboembolism this would raise questions about the validity of attributing the events in the returning passengers to their air travel. Surprisingly high proportions of participants, in whom there was no objective evidence of venous thromboembolism, reported symptoms consistent with deep vein thrombosis (283/869) and pulmonary embolism (87/869). Because it seems unlikely that a control group who had not flown would have reported such high rates, such a finding provides indirect support for the

hypothesis that the prevalence of air travel in the population that gave rise to the cases could have been overestimated in the case-control studies in which people with clinically suspected, but unconfirmed, venous thromboembolism became controls.

Ultimately it is difficult to draw any firm conclusions about the incidence of flight-related venous thromboembolism from these prospective studies of volunteers. First, volunteers are not a representative sample of air travellers and they are likely to have different background risks for venous thromboembolism. Second, the study populations were not comparable and varying proportions of participants were lost to follow-up. Third, the duration of flights differed between studies, as did the number of flights undertaken, the preventive measures that were employed by the participants, and the length of follow-up. Fourth, the type of venous thromboembolic events that were included varied, different approaches were used to diagnose venous thromboembolism, and the potential for diagnostic bias sometimes existed. Finally, pre-existing venous thromboembolism was ruled out before air travel in only some of the studies.

Table 7.6 Incidence of venous thromboembolism in prospective studies of volunteers

Reference	Inclusion criteria	Exclusion criteria	Participants	Air travel	Preventive measures	Exclusion of VTE before travel	Diagnosis of VTE	Proportion who developed VTE
(Arfvidsson et al. 1999)	Delegates who had flown to Pacific Vascular Symposium on Venous Disease in Hawaii.	Local delegates.	83 symposium delegates with interest in flight-related VTE, 49 followed up.	Flights to and from Hawaii (unspecified origin and destination).	31% wore compression stockings.	Duplex US before departure from Hawaii.	Duplex US ≤ 1 week after arrival in Hawaii (83) and ≤ 4 weeks after departure (49).	0/83 DVT after arrival in Hawaii. 1/49 DVT after departure, asymptomatic.
(Scurr et al. 2001)	> 50 years.	VTE in past or at baseline, anticoagulant use, regular use of compression stockings, cardiorespiratory disease, cancer, and other serious illness.	Control group in RCT of compression stockings. 116 in control group, 100 followed up.	Outbound and return non-stop flights ≥ 8 hours within 6 weeks. Median flight time 24 hours.	Nil	Duplex US and D-dimer before outbound flight.	Duplex US and D-dimer ≤ 48 hours after return flight. No further follow-up.	Quoted proportion 12/116 (10% [95% CI 4.8 – 16.0]) DVT calf veins, asymptomatic, D-dimer raised in only 6/12.
(Belcaro et al. 2001) (LONFLIT1, incidence study)	High-risk group inclusions: Past VTE, coagulation disorders, cancer, large varicose veins, severe obesity, and limited mobility.	Low-risk exclusions: High-risk conditions plus recent surgery, travelling with children < 2 years, chronic renal, hepatic, or cardiovascular disease.	***Low-risk group*** 379 enrolled, 355 followed up. ***High-risk group*** 399 enrolled, 389 followed up.	One economy class flight within Northern Hemisphere, no other flights > 2 hours in preceding 2 weeks. Mean flight time 12.4 hours (range 10 – 15).	Nil	Nil	Sonosite US ≤ 24 hours after flight. No further follow-up.	***Low-risk group*** 0/355 DVT ***High-risk group*** 11/389 (2.8%) DVT, not stated whether symptomatic.

Reference	Inclusion criteria	Exclusion criteria	Participants	Air travel	Preventive measures	Exclusion of VTE before travel	Diagnosis of VTE	Proportion who developed VTE
(Belcaro et al. 2001) (LONFLIT2)	"High-risk" passengers as defined in LONFLIT1.	VTE at baseline.	Control group in RCT of stockings. Unclear how many randomised to control group, 422 followed up.	As in LONFLIT1. Mean flight time 12.5 hours (range 10 – 15).	Instructions re exercise, fluid intake, food, and clothing.	Sonosite US ≤ 48 hours before flight.	Sonosite US ≤ 24 hours after flight. No further follow-up.	19/422 (4.5%) DVT, not stated whether symptomatic.
(Cesarone et al. 2002) (LONFLIT3)	"High-risk" passengers as defined in LONFLIT1.	VTE at baseline. Some *inclusion* criteria listed as *exclusion* criteria.	Control group in RCT of aspirin and LMWH. 100 in control group, 82 followed up.	No details provided.	As in LONFLIT2.	Sonosite US unspecified time before flight.	Sonosite US unspecified time after flight. No further follow-up.	4/82 (4.8%) DVT, unclear whether symptomatic.
(Belcaro et al. 2002) (LONFLIT4 Concorde Edema-SSL Study)	"Low-medium risk" passengers.	High-risk passengers as defined in LONFLIT1, also those with other treated medical conditions, > 1.9 metres tall, weight > 90 kg, VTE at baseline.	Control groups in 2 RCTs of stockings. ***1st RCT*** 188 in control group, 179 followed up. ***2nd RCT*** 143 in control group, 135 followed up.	***1st RCT*** One non-stop flight of 7 – 8 hours in economy class. ***2nd RCT*** One non-stop flight of 11 – 12 hours in economy class.	As in LONFLIT2.	Sonosite US unspecified time before flight.	Sonosite US unspecified time after flight. No further follow-up.	<u>7 – 8 hour flights:</u> 4/179 (2.2%) DVT. <u>11 – 12 hour flights:</u> 3/143 (2.1%) DVT. Not stated whether DVT symptomatic.
(Cesarone et al. 2003a) (LONFLIT4 EcoTraS Study)	"Low-medium risk" passengers.	As in LONFLIT4 Concorde Edema-SSL Study.	Control groups in 2 RCTs of stockings. ***1st RCT*** 108 in control group, 98 followed up. ***2nd RCT*** 82 in control group, 71 followed up.	***1st RCT*** One non-stop flight of 7 – 8 hours in economy class. ***2nd RCT*** One non-stop flight of 11 – 12 hours in economy class.	As in LONFLIT2.	Sonosite US unspecified time before flight.	Sonosite US unspecified time after flight. No further follow-up.	<u>7 – 8 hour flights:</u> 0/98 DVT. <u>11 – 12 hour flights:</u> 0/71 DVT.

Reference	Inclusion criteria	Exclusion criteria	Participants	Air travel	Preventive measures	Exclusion of VTE before travel	Diagnosis of VTE	Proportion who developed VTE
(Cesarone et al. 2003b) (LONFLIT4-Venoruton Study)	"Low-medium risk" passengers with uncomplicated varicose veins.	As in LONFLIT4 Concorde Edema-SSL Study.	Control (placebo) group in RCT of hydroxyethyl rutosides. 81 in control group, 70 followed up.	One non-stop flight of 7 – 8 hours in economy class.	As in LONFLIT2.	Sonosite US unspecified time before flight.	Sonosite US unspecified time after flight. No further follow-up.	0/70 DVT.
(Cesarone et al. 2003c) (LONFLIT4-Concorde Deep Venous Thrombosis and Edema Study)	"Low-medium risk" passengers.	As in LONFLIT4 Concorde Edema-SSL Study.	Control groups in 2 RCTs of stockings. ***1st RCT*** 76 in control group, 72 followed up. ***2nd RCT*** 68 in control group, 66 followed up.	***1st RCT*** One non-stop flight of 7 – 8 hours in economy class. ***2nd RCT*** One non-stop flight of 11 – 12 hours in economy class.	As in LONFLIT2	Sonosite US unspecified time before flight.	Sonosite US unspecified time after flight. No further follow-up.	7 – 8 hour flights: 0/72 DVT. 11 – 12 hour flights: 2/66 (3.0%) DVT, not stated whether symptomatic.
(Cesarone et al. 2003d) (LONFLIT-FLITE Trial)	"High-risk" passengers as defined in LONFLIT1.	Anticoagulant or antithrombotic use, VTE or raised D-dimer at baseline. Some *inclusion* criteria listed as *exclusion* criteria.	Control (placebo) group in RCT of pinokinase. 103 in control group, 92 followed up.	One non-stop flight of 7 – 8 hours in economy class.	Shown video re exercise, fluid intake, food, clothing, and stowing of baggage.	Sonosite US ≤ 90 minutes before flight. D-dimer, fibrinogen ≤ 12 before flight.	Sonosite US ≤ 90 minutes after flight. D-dimer, fibrinogen ≤ 4 days after flight.	5/92 (5.4%) DVT, not stated whether symptomatic. 0/5 had raised D-dimer or fibrinogen levels.

Reference	Inclusion criteria	Exclusion criteria	Participants	Air travel	Preventive measures	Exclusion of VTE before travel	Diagnosis of VTE	Proportion who developed VTE
(Belcaro et al. 2003) (LONFLIT5 JAP study)	"High-risk" passengers as defined in LONFLIT1.	> 1.9 metres tall, weight > 90 kg, VTE at baseline. Some *inclusion* criteria listed as *exclusion* criteria.	Control group in RCT of stockings. 114 in control group, 102 followed up.	One non-stop flight of 11.5 – 12 hours in economy class.	Video as in LONFLIT-FLITE trial.	Sonosite US ≤ 90 minutes before flight. D-dimer, fibrinogen ≤ 12 before flight.	Sonosite US ≤ 90 minutes after flight. D-dimer, fibrinogen ≤ 4 hours after flight.	6/102 (5.9%) DVT, not stated whether symptomatic. 0/6 had raised D-dimer or fibrinogen levels.
(Jacobson et al. 2003)	See Table 7.4.	See Table 7.4.	Uncontrolled cohort study of passengers on flights between London and Johannesburg.	One non-stop flight of 11 hours in business or economy class.	Nil.	D-dimer.	D-dimer, duplex US.	74/899 had raised D-dimer levels, but 0/434 had DVT on US.
(Schwarz et al. 2003)	See Table 7.3.	See Table 7.3.	Air travellers in controlled cohort study. 1077 in control group, 964 followed up.	Outbound and return non-stop flights ≥ 8 hours during unspecified period.	Encouraged to exercise and drink plenty of fluids.	D-dimer and US 1 week before outbound flight.	D-dimer and US at 48 hours and 4 weeks after return flight.	7/964 (0.7%) DVT, 5/7 asymptomatic. 20/964 (2.1%) isolated calf muscle venous thrombosis, 19/20 asymptomatic.

Reference	Inclusion criteria	Exclusion criteria	Participants	Air travel	Preventive measures	Exclusion of VTE before travel	Diagnosis of VTE	Proportion who developed VTE
(Hughes et al. 2003) (NZATT Study)	18 – 70 yrs, "low to moderate risk" passengers.	Past VTE, anticoagulant use, pregnancy, contraindications to intravenous contrast, active cancer, recent major surgery or trauma. Raised D-dimer at baseline.	1000 recruited, 83 had raised D-dimer at baseline. Hence 917 eligible, 878 followed up.	Outbound and return non-stop flights ≥ 4 hours within 6-week period. Mean duration of return flight 18.1 hours (SD 5.9).	146 (16.6%) wore compression stockings.	D-dimer ≤ 1 week before outbound flight.	D-dimer ≤ 72 hours and 2 weeks after return flight. Compression US and CTPA (or V-Q scan for all with raised D-dimer levels or high clinical probability symptoms in 3 months after travel (n=112). Follow-up telephone call to 845/878 (96%) at 3 months.	9/878 (1% [95% CI 0.5 – 1.9]) had radiological evidence of DVT or PE in 3 months following flight, all had raised D-dimer levels. 5/9 had symptoms of DVT, 3/8 symptoms of PE, but total number of people with symptoms not stated. 9/9 had total flight time > 24 hours.
(Belcaro et al. 2004)	"High-risk" passengers as defined in LONFLIT1.	As in LONFLIT5 JAP study	Control (placebo) group in RCT of pycnogenol. 105 in control group, 97 followed up.	One non-stop flight of 7 – 12 hours in economy class.	Video as in LONFLIT-FLITE trial.	Sonosite US ≤ 90 minutes before flight.	Sonosite US ≤ 2 hours after flight.	1/97 (1.0%) DVT, asymptomatic. 4/97 (4.1%) SVT, symptomatic.

Abbreviations used in the table CTPA: computed tomography pulmonary angiography, DVT: deep vein thrombosis, LMWH: low-molecular weight heparin, PE: pulmonary embolism, RCT: randomised controlled trial, SD: standard deviation, US: ultrasound, V-Q scan: ventilation-perfusion scan, VTE: venous thromboembolism.

7.4.3 Discussion

In absolute terms, the risk of clinically important venous thromboembolic events following long-distance air travel is uncertain. Surprisingly high rates of asymptomatic venous thrombosis have been reported in volunteers, while studies of symptomatic venous thromboembolism have nearly all involved non-fatal events in passengers requiring medical care on arrival at international airports and so are likely to have underestimated the true incidence. A dose-response relationship has been observed in studies of symptomatic events. The only study to estimate the incidence of fatal events is likely to have provided an underestimate of risk, as it excluded people who died in the community.

7.5 WHAT ARE THE POSSIBLE CAUSAL MECHANISMS OF FLIGHT-RELATED VENOUS THROMBOEMBOLISM?

Research into the possible causal mechanisms of flight-related venous thromboembolism has focused on three main factors: venous stasis, dehydration, and exposure to hypobaric hypoxic conditions. Each of these factors is considered below.

7.5.1 Venous stasis

Venous stasis in air travellers is said to arise from prolonged sitting in cramped conditions, with a consequent reduced function of the calf muscle pump and the possible compression of the popliteal vein against the edge of the seat (Chee and Watson 2005). There is both observational and experimental evidence to support the view that sitting, in general, promotes venous stasis and venous thromboembolism. In 1940, a London forensic pathologist suggested that prolonged sitting was a risk factor for venous thromboembolism after observing a six-fold increase in the number of deaths from pulmonary embolism during the London Blitz (Simpson 1940). Most of the deaths had occurred while sitting in cramped conditions in an air raid shelter, or soon after leaving one. It was concluded that while these people had pre-existing risk factors for venous thromboembolism, the precipitating factor was the prolonged period of immobility in a deck chair or a similar seat — a hypothesis supported by the observation that the number of deaths from pulmonary embolism declined concurrently with the provision of bunks in shelters.

Venous thromboembolism has also been reported in people who had undertaken long journeys by car, bus, truck, train, or ship (Tardy et al. 1993; Eschwège and Robert 1996; Bertos-Polo et al. 2003; Lapostolle et al. 2004; Hitosugi et al. 2005) (and see Appendix C and Table 7.2). In addition, the condition has been described following long periods spent watching television (de Zwaan et al. 1984; Walsh et al. 1986) or sitting at a computer (Beasley et al. 2003; Ng et al. 2003; Beasley et al. 2005). It has also been observed that the appearance of illustrations and accounts of unilateral swelling of the lower limb coincided with the widespread adoption of the chair and a more sedentary lifestyle (Dexter 1973).

Several experiments have recorded a reduction in venous flow in the legs of seated volunteers (Wright and Osborn 1952; Delis et al. 2004). One research group has shown that folds and rings appear in the wall of the popliteal vein when the knee is flexed and these can cause a temporary impairment of venous flow (Schmitt and Mihatsch 1992). Moreover, in recent air and bus travellers with venous thromboembolism, the thrombi appeared to have originated at such folds and rings. It has been suggested that raised intra-abdominal pressure in seated obese passengers might further impede venous return (Arfvidsson et al. 1999). Leg oedema, a sign of venous stasis, has been observed in persons sitting for prolonged periods in normobaric conditions in mock aircraft cabins (Landgraf et al. 1994), office settings (Noddeland and Winkel 1988), lecture theatres (Hollingsworth et al. 2001), and while travelling by bus (Schobersberger et al. 2004). Oedema has also been reported in those travelling by air (Marshall and Dormandy 1987; Loew et al. 1998; Cesarone et al. 2001; Belcaro et al. 2002; Mittermayr et al. 2003; Cesarone et al. 2003a; Cesarone et al. 2003b; Cesarone et al. 2003c; Cesarone et al. 2003d) and the shift of fluid into the interstitial space has been found to continue for up to 24 hours following a flight (Mittermayr et al. 2003). In air travellers, however, it is not possible to disentangle the effects of sitting from the other conditions inherent in flying such as hypobaric hypoxia and possible dehydration.

Venous stasis has been reported to cause endothelial damage (Wu and Mansfield 1980) and has also been associated with increased coagulability, although the results are not consistent. An increase in the viscosity of venous blood has been observed in people who have sat for prolonged periods in normobaric conditions, with some researchers reporting that the increase appeared to be confined to the legs (Moyses et al. 1987;

Hitosugi et al. 2000; Iwama et al. 2002) and others noting signs of systemic haemoconcentration (Hodkinson et al. 2003). A few investigators have drawn blood solely from antecubital veins and have found little or no change in viscosity (Landgraf et al. 1994; Hollingsworth et al. 2001; Stricker et al. 2003; Schobersberger et al. 2004). These inconsistent findings may be due to the small numbers of volunteers involved in the studies, as well as differing methods — for example viscosity has been shown to vary by time of day (Landgraf et al. 1994), the site and method of blood sampling (Moyses et al. 1987; Hamada et al. 2002), and the ambient temperature (Noddeland et al. 1981).

Several investigators have also found signs of increased coagulability in people sitting in normobaric conditions (Iwama et al. 2002; Schobersberger et al. 2004), while others have found no such changes (Tardy et al. 1996) or have measured a reduction in the markers of thrombin generation (Hodkinson et al. 2003; Stricker et al. 2003; Colucci et al. 2004). Increases in platelet packing and in total numbers of platelets have also been described in such conditions (Makris et al. 1986; Hollingsworth et al. 2001).

One group, which observed an increased concentration of lactate in the venous blood of the leg, has proposed that arterial compression and subsequent ischaemia in the seated position also plays a role in the aetiology of flight-related thrombosis (Iwama et al. 2002).

7.5.2 Dehydration

It has been suggested that the relatively low humidity (8 – 12%) encountered on aircraft results in greater insensible and ventilatory fluid losses than occur at higher humidity (Eklof et al. 1996). In addition, an insufficient fluid intake and the diuretic effects of coffee and alcohol can further predispose air passengers to dehydration and a consequent hypercoagulable state. However, as discussed in Chapter 1, the evidence linking dehydration with venous thromboembolism is surprisingly scanty. Moreover, the data regarding dehydration and air travel are inconsistent, with some researchers recording physiological changes consistent with dehydration during real or simulated flight conditions (Carruthers et al. 1976; Simons and Krol 1996) and others finding no such changes (Jacobson et al. 2002; Schobersberger et al. 2002; Mittermayr et al. 2003; Boccalon et al. 2005). One aviation medicine physician has suggested that the low

humidity encountered while flying leads to a subjective, but incorrect, impression of dehydration because of the drying of mucous membranes, conjunctivae, and the skin (Bagshaw 1996).

7.5.3 Hypobaric hypoxia

At usual cruising altitudes, the air pressure in the cabins of modern aircraft is equivalent to that found at altitudes between 1500 and 2400 metres above sea level (Chee and Watson 2005). One consequence of this is that the oxygen saturation of arterial blood decreases during air travel. For example, in a recent study the mean peripheral oxygen saturation in 45 of 84 healthy air travellers dropped to 94% or less at cruising altitude — levels which, according to the researchers, would have prompted the administration of supplemental oxygen in hospitalised patients (Humphreys et al. 2005). Moreover it appears that drowsiness may exacerbate this phenomenon because it impairs the normal increased ventilatory response to hypoxia. In one study, the arterial oxygen saturation of volunteers seated in a hypobaric chamber fell to 80% among those who dozed off and increased again when they were prompted to breathe properly (Simons and Krol 1996).

In the introduction to this chapter, it was revealed that the reported activation of coagulation in hypobaric hypoxic conditions in an uncontrolled experiment (Bendz et al. 2000) received widespread media coverage. However, the findings of that study were questioned because inexplicably high levels of markers of activated coagulation were found before the exposure and, moreover, it is possible that the further increases in these markers during the experiment were artefactual (Bärtsch et al. 2001). The lack of a control group invariably precluded the exploration of these issues.

Two further uncontrolled studies have examined the coagulability of venous blood during air travel, but the results are conflicting. One research group reported an increase in the markers of coagulation activation and a suppression of fibrinolysis during and after an eight-hour flight (Schobersberger et al. 2002). However, since the researchers later observed that coagulation was also activated in bus passengers (Schobersberger et al. 2004), they concluded that stasis, rather than hypoxia, was responsible for the changes in air travellers. Conversely fibrinolysis, which was suppressed in air travellers, was not inhibited in the bus passengers, suggesting that hypoxia had played a role. The second group found no increases in the markers of

activated coagulation, instead observing a reduction in markers of thrombin generation in air travellers (Boccalon et al. 2005). As discussed earlier, such a change had also been observed in seated volunteers in normobaric conditions (Hodkinson et al. 2003; Stricker et al. 2003; Colucci et al. 2004).

Several researchers have conducted small cross-over trials, in which volunteers were exposed alternately to normobaric hypoxic and non-hypoxic conditions, and have concluded that hypoxia does not stimulate activation of coagulation (Crosby et al. 2003; Hodkinson et al. 2003; Dick et al. 2004). One group found no significant change in the markers of coagulation in either exposure situation (Crosby et al. 2003), another found an increase in markers in both situations but no significant differences between hypoxic and control conditions (Hodkinson et al. 2003), and the third simply reported that there were no differences between the two exposures (Dick et al. 2004). In a fourth trial, there were no signs that hypobaric hypoxic conditions stimulated platelet activation or reactivity (Jones et al. 2004).

Research into the possible effects of hypoxia on coagulation has also focused on mountaineers and others exposed to high altitudes, but the results are inconsistent. Signs of increased thrombin generation and inhibition of fibrinolysis at high altitude were described in one recent study (Mannucci et al. 2002), while another found no such changes (Bärtsch et al. 2001).

Other possible effects of hypobaric hypoxia have also been discussed. In one review it was suggested that in-flight hypoxia and the subsequent re-oxygenation might cause endothelial damage (Keynan et al. 2006). It has also been suggested that in air travellers with pre-existing small pulmonary emboli, hypoxia-induced pulmonary vasoconstriction around the embolism might trigger a fatal event (Cheung and Duflou 2001).

7.5.4 Is venous stasis or hypobaric hypoxia to blame?

Two recent cross-over trials, conducted under the auspices of the WHO Research Into Global Hazards of Travel (WRIGHT) initiative, have attempted to disentangle the potential effects of hypobaric hypoxia and immobility on the coagulability of blood (Schreijer et al. 2006; Toff et al. 2006). In the first trial, markers of activated

coagulation and fibrinolysis were measured before, during, and after eight-hour exposures of the 71 participants to air travel (immobility in hypobaric hypoxia), a movie marathon (immobility in normobaric conditions), and usual daily activities (Schreijer et al. 2006). The experiments were separated by two-week intervals and occurred at the same time of day to control for circadian rhythm. Air travel, but not the two normobaric exposures, was associated with an increase in the median concentrations of one of the two measured markers of activated coagulation (thrombin-antithrombin complex). This increase was particularly evident in oral contraceptive users who were carriers of the factor V Leiden mutation. Consistent with previous studies (Hodkinson et al. 2003; Stricker et al. 2003; Colucci et al. 2004; Boccalon et al. 2005), the median value of the another marker of activated coagulation (prothrombin fragment 1 and 2) decreased after both flying and sitting in the cinema and this exceeded the small decrease observed after daily activities which was probably due to circadian changes. It has been suggested that such a change might inhibit the activation of protein C, an important inhibitor of coagulation (Stricker 2006). A few volunteers had very large increases in the two markers of coagulation and the marker of fibrinolysis (D-dimer). The researchers concluded that flying led to an activation of coagulation and fibrinolysis in some susceptible individuals (such as oral contraceptive users with the factor V Leiden mutation) due to some mechanism over and above the effect of immobilisation.

The second cross-over trial produced conflicting results (Toff et al. 2006). In this study, 73 healthy volunteers sat for eight hours in a hypobaric chamber on two occasions at least a week apart. On one of those occasions, the chamber was depressurised to hypobaric hypoxic conditions. Overall, no differences between the hypoxic and the control conditions were found in measures of coagulation, fibrinolysis, platelet function, or markers of endothelial activation. The investigators reported that although there were some changes in a few clotting parameters in both groups, some of which were attributable to normal circadian changes and others to prolonged sitting, there was no significant change in the endogenous thrombin potential, a global marker of coagulation. The researchers thus concluded that there was no support for the hypothesis that hypobaric hypoxia causes a prothrombotic state in people at low risk of venous thromboembolism.

An editorial, which discussed both cross-over trials, concluded that mild hypoxia combined with prolonged sitting does not produce a hypercoagulable state in healthy air travellers, although there does appear to be an interaction between these factors and oral contraceptive use and the factor V Leiden mutation (Bärtsch 2006).

7.5.5 Discussion

Several possible causal mechanisms have been proposed to explain the increased risk of venous thromboembolism in air travellers, such as venous stasis, dehydration, and exposure to hypobaric hypoxic conditions. Experimental studies, involving volunteers exposed to real or simulated aeroplane cabin conditions, have confirmed the role of venous stasis but have provided mixed results regarding the role of dehydration and the possible activation of coagulation in hypobaric hypoxic conditions. These inconsistent results may be due to the small numbers of volunteers involved in the studies and differences in methods. However, there is also evidence to suggest that activation of coagulation in response to hypoxia may only occur in some people — for example, oral contraceptive users and carriers of the factor V Leiden mutation.

7.6 CAN FLIGHT-RELATED VENOUS THROMBOEMBOLISM BE PREVENTED?

Much of the early information about how to avoid flight-related venous thromboembolism appears to have been derived from assumptions about the causal mechanisms and the extrapolation of data from other settings, rather than being based on any firm evidence. The authors of the initial case reports and case series stressed the importance of leg exercises (Homans 1954), moving about the cabin (Beighton and Richards 1968), adequate fluid intake (Symington and Stack 1977), and the avoidance of alcohol (Holliday 1985) when flying. Aspirin was recommended for high-risk passengers (Holliday 1985), as were compression stockings and subcutaneous heparin (Bounameaux 1988). The use of devices which exercised the lower legs were also promoted (Coller 1988).

Since these early reports, reviewers have continued to advocate general preventive measures to avoid venous stasis and dehydration such as walking about the aircraft cabin, performing leg exercises while seated, avoiding sedating drugs, abstaining from

alcohol, and ensuring a generous intake of other fluids (Bärtsch 2006; Stricker 2006). However the evidence for such measures remains limited and not all are without risk — for example, unexpected turbulence may be encountered while moving about the cabin (Gallus and Baker 2001). Some researchers have found that regularly exercising the calves when seated reduces oedema (Noddeland and Winkel 1988), while others have not (Landgraf et al. 1994). A substantial increase in venous return has been measured in persons using a bipedal device to alternately plantar flex and dorsi flex the feet (Caruana et al. 2003). It has also been suggested that compliance with recommended leg exercises could be enhanced by the use of accelerometers to monitor calf muscle pump activity (O'Donovan et al. 2005). Intermittent pneumatic compression of the lower limbs has been shown to suppress procoagulant activity and enhance global fibrinolytic potential in seated volunteers and hence may have some implications for the prevention of flight-related venous thromboembolism (Giddings et al. 2004).

As discussed earlier, it is unclear whether dehydration occurs during long-distance air travel. However, in one randomised controlled trial conducted in simulated flight conditions, the consumption an electrolyte-carbohydrate drink was associated with a more favourable net fluid balance than drinking plain water (Hamada et al. 2002). Moreover, the viscosity of venous blood in the legs remained normal in the intervention group whereas it increased in the plain water group.

Passengers with pre-existing risk factors for venous thromboembolism have usually been advised to see their doctor to determine the need for additional preventive measures (Chee and Watson 2005). Several randomised controlled trials have shown that below-knee compression stockings help to prevent ultrasound-detected asymptomatic deep vein thrombosis in air travellers (Belcaro et al. 2001; Scurr et al. 2001; Belcaro et al. 2002; Belcaro et al. 2003; Cesarone et al. 2003c), although the clinical relevance of such thrombi is unknown. Compression stockings have also been shown to reduce oedema during long-distance flights (Loew et al. 1998; Belcaro et al. 2002; Cesarone et al. 2003a; Cesarone et al. 2003c) and prolonged sitting in normobaric conditions (Hollingsworth et al. 2001; Iwama et al. 2002). In one trial, in which participants wore a stocking on just one leg, increases in viscosity and lactate, and a decrease in coagulation time, were observed solely in the leg without a stocking (Iwama et al. 2002).

In a recent Cochrane systematic review of the above trials, it was estimated that the use of compression stockings reduced the odds of developing asymptomatic deep vein thrombosis by about 90% and decreased the incidence of such events from 10 – 30 per 1,000 to 1 – 3 per 1,000 passengers on flights of more than four hours (Clarke et al. 2006). The reviewers concluded that stockings also helped to prevent superficial venous thrombosis, although an increased incidence of thrombophlebitis was reported in one study (Scurr et al. 2001). However, it was not possible to determine whether stockings reduced the occurrence of more clinically relevant symptomatic deep vein thrombosis, non-fatal pulmonary embolism, or death because none of the trial participants had suffered these outcomes.

Opinion about the prophylactic role of aspirin has been divided. Some commentators have supported its use in air travellers (Kesteven 2000; Bagshaw 2001; Geroulakos 2001; British Thoracic Society Standards of Care Committee 2002), while others have maintained that it should not be promoted because of a lack of efficacy and the risk of adverse reactions such as gastrointestinal discomfort, bleeding complications, and hypersensitivity (Gallus and Baker 2001; MacGillavry et al. 2001; Giangrande 2002; Makris 2002; Possick and Barry 2004; Chee and Watson 2005; Stricker 2006). For example, one randomised controlled trial not only failed to show that aspirin was beneficial in preventing asymptomatic deep vein thrombosis in air travellers, but 13% of treated participants suffered from mild gastrointestinal discomfort (Cesarone et al. 2002). In a second randomised controlled trial conducted in normobaric conditions, the total platelet count was reduced in participants who had taken aspirin one hour earlier, however no measurements were made before the aspirin was dispensed (Hollingsworth et al. 2001). Despite a lack of information about its effectiveness, the "number needed to treat" has been estimated for the prophylactic use of aspirin in air travellers (Loke and Derry 2002). Assuming an incidence of flight-related deep vein thrombosis of 20 per 100,000 passengers, and that the beneficial effect of aspirin observed in patients with hip fractures would also apply for air travellers, 17,000 passengers would need to be treated with a single dose of aspirin to prevent one case.

The use of prophylactic low-molecular weight heparin for air travellers with a high background risk of venous thromboembolism has been more widely accepted (Forbes and Johnston 1998; Kesteven 2000; Bagshaw 2001; Gallus and Baker 2001; Geroulakos

2001; British Thoracic Society Standards of Care Committee 2002; Giangrande 2002; Makris 2002; Possick and Barry 2004; Chee and Watson 2005; Bärtsch 2006; Stricker 2006), although some commentators have expressed concern regarding the lack of information about its effectiveness and safety in air travellers (MacGillavry et al. 2001). One randomised controlled trial of a single dose of low-molecular weight heparin before a long-distance flight showed a reduced risk of asymptomatic deep vein thrombosis (Cesarone et al. 2002). In another trial, of volunteers confined to a hypobaric hypoxic environment, low-molecular weight heparin reportedly prevented the activation of coagulation in the participants (Bendz et al. 2001) — although the trial did not include a control group, so it is impossible to know whether coagulation was indeed prevented or whether hypobaric hypoxic conditions simply do not provoke changes in coagulability.

Several small randomised controlled trials have also examined the prophylactic potential of various herbal preparations. For instance, a decreased incidence of asymptomatic deep vein thrombosis or superficial venous thrombosis was reported in air travellers treated with pinokinase (Cesarone et al. 2003d) and pycnogenol (Belcaro et al. 2004). Similarly, oedema was apparently reduced in passengers who received an extract of horse chestnut seed (Marshall and Dormandy 1987), a *Centella asiatica* preparation (Cesarone et al. 2001), hydroxyethyl rutosides (Cesarone et al. 2003b), and pinokinase (Cesarone et al. 2003d), while a dried extract of vine leaves had no observable effect on oedema (Loew et al. 1998).

Finally, secondary prevention obviously has an important role in the prevention of fatal venous thromboembolic events following long-distance air travel. As such, medical staff at airports need to be aware of the possible significance of symptoms such as leg pain or swelling, transient shortness of breath, chest pain, and syncope in recent arrivals. Moreover, because symptoms may not develop immediately after disembarking from aircraft, similar vigilance is required from doctors in other settings.

CHAPTER 8 DESCRIPTIVE STUDY OF LONG-DISTANCE AIR TRAVEL: OBJECTIVES AND METHODS

8.1 INTRODUCTION

The possible relationship between air travel and venous thromboembolism is of particular relevance to New Zealand because of its relative geographical isolation, because most people travel to and from the country by air, and because increasing numbers of New Zealand residents and overseas visitors are undertaking such journeys. According to the national statistics office, Statistics New Zealand, by 1970 about 90% of travellers arrived in New Zealand by air (Statistics New Zealand 2001a). In 2000 almost all arrivals were by air (Table 8.1).

Table 8.1 Arrivals in New Zealand in the year to May 2000 by mode of travel*

Mode of travel	Short-term migrants (number [%])		Permanent and long-term migrants§ (number [%])
	New Zealand residents†	Overseas visitors‡	
Air	1,223,711 (98.5)	1,633,854 (97.2)	60,082 (97.7)
Sea	1,421 (0.1)	12,530 (0.8)	239 (0.4)
Unspecified	17,820 (1.4)	34,203 (2.0)	1,196 (1.9)
Total	**1,242,952**	**1,680,587**	**61,517**

* Data provided by Statistics New Zealand.
† Defined by Statistics New Zealand as New Zealand residents who arrived from overseas after an absence of less than 12 months.
‡ Defined by Statistics New Zealand as overseas visitors who intended to stay in New Zealand for less than 12 months.
§ Defined by Statistics New Zealand as overseas migrants who intended to stay in New Zealand for 12 months or more (including permanently) and New Zealand residents who returned after an absence of 12 months or more.

With the exception of flights from neighbouring Pacific Island nations and the east coast of Australia (three to four hour flights), and from other parts of Australia (five to eight hour flights), air passengers who arrive in New Zealand have all undertaken journeys with total flight times of more than eight hours, and in many cases more than 24 hours. In the year to May 2000 for example, data obtained from Statistics New Zealand show that at least 994,508 (34.1%) of the 2,917,647 passengers who arrived in New Zealand by air had flown for more than eight hours (Table 8.2). This is likely to be a conservative estimate for two reasons. First, the port of embarkation refers to the airport where the passenger first boarded the aircraft on which they arrived in New Zealand and this is not necessarily the airport from which they began their journey. For example, a passenger travelling from the UK to New Zealand who changed aircraft at one of the main transfer ports (in Los Angeles, Singapore, or Sydney) would record that airport as their port of embarkation (Statistics New Zealand 2001a). Second, the estimated flight times in Table 8.2 represent the shortest journeys from the ports of embarkation to New Zealand. These flight times were obtained by searching the schedules of two major networks of international airlines[2] to find the most direct flights to Auckland International Airport — the airport at which 71% of international travellers arrived in 2000 (Statistics New Zealand 2001a).

[2] "Star alliance" (http://www.staralliance.com) and "oneworld alliance" (http://www.oneworldalliance.com).

Table 8.2 Arrivals in New Zealand by air in the year to May 2000, by port of embarkation*

Estimated flight time† and port of embarkation‡	Short-term migrants		Permanent and long-term migrants¶
	New Zealand residents§	Overseas visitors‖	
Flight time ≤ 4 hours			
Brisbane	249,299	160,595	3,980
Coolangatta	7,294	2,567	95
Cairns	6,453	6,564	101
Melbourne	154,964	199,253	3,240
Sydney	330,785	496,584	10,275
Apia	19,339	16,045	1,276
Niue	210	80	8
Norfolk Island	6,612	1,150	38
Noumea	7,252	8,812	20
Pago Pago	-	234	-
Rarotonga	16,463	12,070	520
Tonga	10,326	10,707	559
Port Vila	7,032	2,002	57
Nadi	71,962	42,910	2,023
Suva	5,581	3,684	428
Other South Pacific airports	5,555	11,470	115
Total (number [%])	**899,127 (73.5)**	**974,727 (59.7)**	**22,735 (37.8)**
Flight time 5 – 7 hours			
Adelaide	-	14	-
Perth	10,438	15,317	781
Total (number [%])	**10,438 (0.9)**	**15,331 (0.9)**	**781 (1.3)**
Flight time 8 – 11 hours			
Denpasar**	5,601	5,406	794
Hong Kong**	31,614	64,178	5,812
Honolulu	20,466	16,131	667
Kansai	5,428	34,385	1,484
Kuala Lumpar	21,304	33,598	4,268
Nagoya**	1,048	12,850	284
Narita**	9,942	59,913	1,795
Singapore	75,970	141,500	8,511
Taipei	11,622	22,685	823
Total (number [%])	**182,995 (14.9)**	**390,646 (23.9)**	**24,438 (40.7)**

Estimated flight time[†] and port of embarkation[‡]	Short-term migrants		Permanent and long-term migrants[¶]
	New Zealand residents[§]	Overseas visitors[‖]	
Flight time 12 – 15 hours			
Bangkok	11,362	12,716	640
Beijing	-	39	30
Buenos Aires	4,579	9,941	292
Fukuoka	-	4,076	-
Los Angeles	90,781	150,880	6,467
Seoul	13,022	51,627	2,875
Shanghai	-	199	24
Vancouver	280	781	6
Total (number [%])	**120,024 (9.8)**	**230,259 (14.1)**	**10,334 (17.2)**
Flight time ≥ 16 hours			
Chicago	187	173	5
Frankfurt[††]	449	4016	62
Heathrow[††]	10,334	17276	1,549
Gatwick[††]	157	1,426	178
Total (number [%])	**11,127 (0.9)**	**22,891 (1.4)**	**1,794 (3.0)**
Total arrivals by air	**1,223,711**	**1,633,854**	**60,082**

[*] Data provided by Statistics New Zealand.
[†] Shortest flight time between port of embarkation and Auckland International Airport.
[‡] Defined by Statistics New Zealand as the airport or country in which the migrant first boarded the aircraft on which they arrived in New Zealand.
[§] Defined by Statistics New Zealand as New Zealand residents who arrived from overseas after an absence of less than 12 months.
[‖] Defined by Statistics New Zealand as overseas visitors who intended to stay in New Zealand for less than 12 months.
[¶] Defined by Statistics New Zealand as overseas migrants who intended to stay in New Zealand for 12 months or more (including permanently) and New Zealand residents who returned after an absence of 12 months or more.
[**] Shortest flight time less than 12 hours, but some flight times ≥ 12 hours.
[††] Shortest flight time less than 24 hours, but some flight times ≥ 24 hours.

Travel to and from New Zealand not only involves long flights, but increasing numbers of such journeys are being undertaken by New Zealanders of all ages. Statistics New Zealand migration data reveal that in the year to May 1990, 726,163 New Zealand residents (21.5% of the estimated resident population of 3,379,250[3]) arrived back in the country by air after an absence of less than twelve months, as compared with 1,268,388 residents (33.1% of the estimated resident population of 3,832,930[4]) in 2000 (Table 8.3). These figures may reflect a greater number of New Zealanders travelling overseas, or an increase in the number of overseas trips undertaken by certain individuals, or both.

The annual number of arrivals by short-term overseas visitors also increased substantially between 1990 and 2000, from 964,690 to 1,775,530 (Table 8.4). In contrast to the New Zealand residents who travelled internationally, many of whom visited Australia or neighbouring Pacific Islands, overseas visitors tended to have undertaken longer flights. In the year to May 2000, at least 40% of short-term overseas visitors arrived in New Zealand after flights of more than eight hours, as compared with at least 26% of the New Zealand resident short-term arrivals (Table 8.2).

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[3] Estimated population on 31 December 1990, derived from census data and obtained from Statistics New Zealand

[4] Estimated population on 31 December 2000, derived from census data and obtained from Statistics New Zealand

Table 8.3 Arrivals of New Zealand residents by air, after an absence of less than 12 months, in the years to May 1990 and May 2000 *

Age (years)	1990	2000
Under 5	18,521	35,340
5 - 9	19,565	40,988
10 – 14	25,634	46,181
15 – 19	40,048	53,389
20 – 24	57,679	74,377
25 – 29	66,668	105,275
30 – 34	66,646	122,995
35 – 39	69,665	138,318
40 – 44	78,596	131,375
45 – 49	69,286	133,664
50 – 54	56,647	130,245
55 – 59	46,685	92,707
60 – 64	44,248	62,949
65 – 69	32,079	43,556
70 – 74	18,747	29,950
75 – 79	10,954	18,249
80 – 84	3,383	6,565
85 – 89	923	1,807
90 – 94	142	432
95 Years and Over	47	26
Total	**726,163**	**1,268,388**

* Data provided by Statistics New Zealand.

Table 8.4 Arrivals of overseas visitors by air, who intended to stay for less than 12 months, in the years to May 1990 and May 2000*

Age (years)	1990	2000
0-14	75,130	145,713
15-19	42,442	81,265
20-24	91,731	132,447
25-29	130,162	201,463
30-34	101,351	185,341
35-39	88,839	163,212
40-44	91,092	150,743
45-49	76,936	154,092
50-54	65,306	158,599
55-59	56,687	133,937
60 and over	145,014	268718
Total	**964,690**	**1,775,530**

* Data provided by Statistics New Zealand.

In July 2000, it was decided to undertake a population-based study in New Zealand to explore the potential association between long-distance air travel and venous thromboembolism. As described in Chapter 7, at that time the evidence for a link was purely circumstantial; the published data comprised case reports, case series, and one poorly designed case-control study in which a four-fold significant risk of venous thromboembolism was found for travel by any mode of transport. The decision to undertake a study was prompted by this lack of information and the particular relevance of any association between air travel and venous thromboembolism both for individual travellers and for the providers of medical services in New Zealand. Since venous thromboembolism is a relatively rare event and the population of New Zealand is small, a case-control study was considered the most appropriate analytical study design to explore the possible association.

Initially descriptive and case-control studies involving people admitted to hospital with deep vein thrombosis or pulmonary embolism were planned. However, as was discussed at the beginning of Chapter 7, the possible link between long-distance air travel and venous thromboembolism received widespread media attention in late 2000 and early 2001. In light of the subsequent public and professional concern about the potential association, the proposed hospital-based prospective research was no longer feasible because of the potential for referral and diagnostic biases. While a study confined to severe cases might have avoided these problems, such an investigation would have taken many years to complete given the relative rarity of such events and the size of the New Zealand population. On the other hand, a study of people who had already died from pulmonary embolism was feasible. Moreover, while concerns were expressed in the media and elsewhere about deaths in air travellers, none of the published epidemiological studies had explored the relative or absolute risks of dying from pulmonary embolism following a long-distance flight. Hence, a study involving fatal cases of pulmonary embolism (initiated at the end of 2002) was undertaken to examine these risks.

There were two components to the research: a descriptive study of men and women aged 15 – 59 years who died from pulmonary embolism in New Zealand between 1 January 1990 and 31 December 2000, and a national case-control study which was based on a subset of the cases included in the descriptive study. The research was confined to

people aged 15 – 59 years because the majority (77%) of people who arrived in New Zealand on international flights during the study period were within this age range (data provided by Statistics New Zealand). The methods of the descriptive study are outlined in this chapter, and the results are presented and discussed in the next chapter. The methods of the case-control study are explained in Chapter 10, and the results and discussion follow in Chapter 11.

8.2 DEFINITION OF LONG-DISTANCE AIR TRAVEL

In both the descriptive and the case-control studies, long-distance air travel was defined as a flight of at least three consecutive hours. If a journey consisted of more than one flight, the total flight time for the journey was calculated by adding together the duration of each flight (but at least one flight had to be three or more consecutive hours). A minimum flight time of three hours was chosen for several reasons. First, it allowed comparisons with the studies published at the time the present research was initiated, which had all examined the risk of venous thromboembolism following journeys of at least three or four hours' duration (Ferrari et al. 1999; Kraaijenhagen et al. 2000; Arya et al. 2002). Second, since domestic air travel within New Zealand involves flight times of less than three hours, while international flights to and from New Zealand involve journeys of at least three consecutive hours, such a definition simply required study participants to recall international travel during the relevant period. This had several potential advantages. It would be unlikely that cases and controls who had never left New Zealand would be incorrectly classified as having undertaken a long-distance flight. Next of kin would be likely to remember an international flight undertaken by their relative in the weeks before they became unwell, and controls who travelled very rarely would also be likely to recall such an event. For similar reasons, it is likely that any domestic flights within countries other than New Zealand that had involved flight times of more than three hours would be identified. While controls who travelled frequently might have difficulties recalling details of flights, such travel could often be verified by reference to passports and other personal records. Finally, a three-hour definition was appropriate because the absolute risk of dying from pulmonary embolism following a long-distance flight was to be estimated using data from Statistics New Zealand about international arrivals data as the denominator. While

the total duration of travel undertaken by arriving passengers cannot be accurately established using these data, it is clear that people arriving on international flights must have flown for at least three hours. As discussed in Chapter 2, the date of onset of the fatal episode was taken as an index date.

8.3 OBJECTIVES

The objectives of the descriptive study were as follows:

1. To determine the proportion of individuals who died from pulmonary embolism in New Zealand between 1990 and 2000 who had undertaken long-distance air travel during the four weeks before the onset of the fatal episode.
2. To estimate the absolute risk of dying from pulmonary embolism following a long-distance flight.
3. To compare the sex and age-adjusted mortality rate from pulmonary embolism in a population in which almost all people had recently undertaken long-distance air travel (overseas visitors to New Zealand) with the rate in a population where few would recently have travelled (the resident population of New Zealand).
4. To examine the possibility that the overall health status of overseas visitors differed from that of New Zealand residents by comparing mortality from all causes in the overseas visitor population with the rate in the resident population of New Zealand.

The four-week period was chosen to allow comparisons with the analytic studies that had been published at the time the research was initiated (Ferrari et al. 1999; Kraaijenhagen et al. 2000; Samama and the Sirius Study Group 2000; Arya et al. 2002).

8.4 METHODS

8.4.1 Case ascertainment

As discussed in Chapter 2, there were 41 men and 80 women aged 15 – 59 years who died in New Zealand between January 1990 and December 2000 for whom pulmonary embolism was considered the underlying cause of death. Of these 121 cases, eight were short-term overseas visitors to New Zealand and 113 were normally resident in New Zealand on the index date. According to existing records and information from next of kin, none of the 113 "normally resident" cases were recent "permanent or long-term migrants" (as defined by Statistics New Zealand). All of the 121 cases were included in the case series.

8.4.2 Sources of information about long-distance air travel

Information about long-distance air travel in the four weeks before the index date was sought from the next of kin of cases, as well as from existing records. The latter included coroners' and police records, death certificates, and hospital, general practitioner, mental health, and family planning clinic records as described in Chapter 2. The details of journeys of at least four hours' duration by other means of transport in the four weeks before the index date were also obtained from existing records and from next of kin.

8.4.3 Identifying next of kin

Table 8.5 shows the sources of information that were used to identify next of kin. As outlined in Chapter 2, the underlying cause of death in 105 of the 121 cases was certified by a coroner and for 16 cases a death certificate was completed by a doctor. For 102 of the 105 coroner-certified deaths, the Police 47 or Statement of Identification forms provided the name, relationship, address, and phone number of at least one next of kin. Of the remaining three coroners' cases, no relatives were identified in the coroner's records of the first case, a homeless alcoholic man. During a brief hospital admission a few weeks before his death, he told hospital staff that he had no relatives or friends that could serve as next of kin. The coroner's and hospital records also failed to identify the next of kin of the second case, a Swiss tourist. Attempts to obtain this information from the police and the Swiss Embassy in Wellington were unsuccessful because the relevant police files had recently been destroyed and the Embassy had no

record of his death. The name and contact details of a sibling were eventually obtained by Swiss medical contacts. The coroner's records of the third case identified a mental health worker, but no next of kin. This information was found in hospital records. For 12 of the 16 doctor-certified deaths, a Notification of Death for Registration form was appended to the Medical Certificate of Causes of Death. This form contained the names and occupations of the parents of the case, the names and ages of any former or current spouses, and the sex and age of any offspring. For the remaining four cases, next of kin details were obtained from hospital records. Hence, the next of kin of all but two cases were identified using existing records.

Table 8.5 Sources of information used to identify the next of kin of New Zealand residents and overseas visitors

Source of information	New Zealand residents	Overseas visitors	Total
Coroners' records	96	6	102
Notification of Death for Registration forms	12	-	12
Hospital records	4	1	5
Other	-	1	1
No next of kin identified	1	-	1
Total	**113**	**8**	**121**

8.4.4 Obtaining the current contact details for next of kin of New Zealand residents

Although the existing records generally contained the contact details of next of kin, this information was compiled up to 13 years before the study was initiated. In order to obtain the current contact details of the relatives of New Zealand cases, an electronic copy of the current New Zealand Parliamentary Electoral Roll ("the electoral roll") and the on-line national telephone directory were searched. Unfortunately, it was not possible to obtain a telephone number for all the next of kin for several reasons. First, people can choose not to have their home address and telephone number listed in the telephone directory. Second, even if a household number is listed, the entry usually just includes the name(s) of the account holder(s), rather than the names of all the people living in the household. Finally, many mobile telephone numbers are not listed in the directory.

Before describing the search of the electoral roll in more detail, it is necessary to provide some background information about the roll. By law, all New Zealand citizens and permanent residents aged 18 years and over who have lived in New Zealand continuously for at least one year are required to enrol to be registered on the electoral roll (Elections New Zealand 2005a). People who are concerned that their life could be in danger if their details appeared on the publicly available roll and have supporting documents such as a protection order, can apply to be enrolled on a confidential unpublished roll (Elections New Zealand 2005a). A Registrar of Electors within each electorate is responsible for maintaining and updating the electoral roll on a daily basis, and for conducting enrolment update campaigns before major elections (Elections New Zealand 2005b). The Registrars receive change of address information from electors (directly or through change of address forms submitted to New Zealand Post), and information about name changes and deaths from the office of Births, Deaths, and Marriages (Elections New Zealand 2005a). At any one time, only a very small proportion of the eligible population will not be registered on the electoral roll. As of 17 June 2005, for example, about 8% of eligible citizens and residents (estimated from census data) were not enrolled (Elections New Zealand 2005c).

An annually updated paper copy of the electoral roll is available for public inspection at local Registrars' offices, and copies of the current and previous rolls are held by the Hocken Library at the University of Otago. Approved health researchers are also able

to obtain an electronic copy of the electoral roll at any time from the Electoral Enrolment Centre in Wellington (Elections New Zealand 2005b). Unlike paper versions of the roll, the age of each elector is included in the electronic version. Moreover, it is possible to search the electronic roll using any of the following fields: name, age in individual years, sex, occupation, residential and postal addresses, and electorate.

For the present research, it was possible to refer to electronic copies of the electoral roll (General and Maori[5] combined) for the years 1993, 1996, 1998, 2000, 2002, and 2003. To find the current addresses of the next of kin of the New Zealand cases, the 2002 and 2003 (when it became available) electronic rolls were searched by name. Spouses, partners, or other adult family members with whom the case had lived on the index date were considered the most appropriate next of kin to approach. For cases who did not live with a family member, contact details of the closest named relative were sought. If the next of kin who were being sought were not found on the latest electoral roll or in the telephone directory, electoral rolls from earlier years were searched to determine the year in which they were last enrolled. Enquiries were then made with Births, Deaths, and Marriages to ascertain whether the person had died or changed their name after this date. In situations where the next of kin had died or there was no record of a name change, and other methods had failed to locate them, the contact details of the next named relative were sought. If there were no other named next of kin, the electoral roll was searched by address to identify others living at the same address as the case (or the named next of kin) before or on the index date. Official birth records held by the Hocken Library were also examined to identify the children of female cases.

Of the 112 New Zealand cases for whom next of kin were identified, the postal address of at least one next of kin was found on the electoral roll for 107 of the cases. The wife of a further case was located by searching the telephone directory. The wives of another three cases were subsequently found to have remarried and changed their surnames. One marriage was identified by the office of Births, Deaths, and Marriages and the next

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[5] Maori can choose to be enrolled on either the General Parliamentary Electoral Roll or the Maori Parliamentary Electoral Roll.

of kin's new surname and address was recorded on the marriage certificate. The second woman, who remarried overseas, was found with the assistance of her deceased husband's general practitioner who obtained her new contact details from her son. The third woman had previously been contacted during the case-control study of psychotropic drugs, but a letter sent to her previous address was returned marked "gone, address unknown". Her new address was obtained, with her permission, from the real estate agent who had sold her house. The husband of the remaining case was located with the assistance of his general practitioner, who forwarded the invitation letter to him and provided his telephone number.

8.4.5 Obtaining the current contact details for next of kin of overseas visitors

Several methods were used to locate the next of kin of the cases who died while visiting New Zealand. The father of one woman was found on the Australian electoral roll and the on-line Australian telephone directory. The Taiwanese, Swiss, and UK on-line telephone directories provided the addresses and telephone numbers of the cousin and brothers of three further cases. The hospital records of a man who lived in Australia contained the address of relatives who lived in New Zealand. By searching for this address on past electoral rolls, the names of these relatives were found, as was their new address. A letter addressed to the wife of the case was then sent to their residence. The hospital records of a Tongan woman contained both the name and address of a New Zealand relative. As this relative was not found on later electoral rolls, earlier rolls were searched by address to identify others who had lived in the household. The new address of one relative, a sister-in-law, was found on the 2003 electoral roll.

Attempts to trace the husbands of the two remaining overseas cases were unsuccessful. These attempts included engaging the assistance of research colleagues in the UK, and contacting the Japanese Consulate-General and a former travel agent who was listed as the New Zealand contact of one of the women. Thus, for three cases (including the New Zealand case with no identified next of kin), no next of kin were traced.

8.4.6 Contacting next of kin

A letter was sent to the next of kin in New Zealand and overseas, inviting them to take part in the study. When this research was first planned, a decision was made not to ask

next of kin specific questions about the circumstances of their relative's death because such information was already available from existing records and hence not subject to recall bias. Moreover it was felt that some next of kin might be reluctant to participate if they thought that they would be asked to recount such a distressing event to a stranger. The letter of invitation, therefore, indicated that the interview would involve questions about the life of their relative before they became unwell.

One of two standard letters was sent to the next of kin of the New Zealand residents, according to whether contact had previously been made to enquire about the name of their relative's general practitioner during the case-control study described in Chapters 4 – 6 (Appendix A, letters 19 and 20). For the next of kin of the overseas visitors, one of two standard letters were also sent, depending on whether it was thought likely that they spoke English fluently (Appendix A, letters 21 and 22). The second of the letters asked the recipient to indicate in which language they would prefer to conduct any telephone conversations. One letter was translated into Taiwanese at the outset by a final-year medical student, who advised that it was unlikely that the next of kin would understand the letter of invitation if it was written in English.

All next of kin were asked to return, in a reply-paid envelope, a form recording their contact details and suitable times to be contacted by telephone. Those who returned the form were telephoned by me at the designated time to discuss the study and oral consent was sought for a telephone interview (Appendix D, form 1). On the other hand, if no reply was received after two weeks, next of kin were contacted by telephone (Appendix D, form 2). Those who did not have a traceable telephone number were sent up to two further letters (Appendix A, letter 23). Since it was impossible to know whether a lack of response was due to an unwillingness to participate or simply that the next of kin had changed address, a letter was sent to a relative at another address if no reply was received after a maximum of three letters. For next of kin who agreed to participate in the study, a time of their choosing was made for a telephone interview.

The initial and subsequent letters, reply-paid forms, and oral consent forms were adapted from those employed in two previous case-control studies in which response rates were high (Paul et al. 1989; Cox et al. 2002).

8.4.7 Telephone interviews with next of kin

Computer-assisted telephone interviews were undertaken using a standardised questionnaire, as will be described in detail in Chapter 10. Briefly, the questionnaire included questions about any international flights undertaken in the four weeks before the index date and domestic flights undertaken in countries other than New Zealand during the same period. Demographic data and information about other risk factors for venous thromboembolism were also sought. In addition, next of kin were asked about journeys of at least four hours' duration undertaken by their relative using other means of transport during the four weeks before the index date. While next of kin were not asked specific questions about the course of their relative's fatal condition, many volunteered this information.

All of the interviews were undertaken by a registered nurse (Ms Sue McAllister) or me, except for interviews with the next of kin of two overseas visitors. One of these interviews was conducted in Swiss German by a Specialist Physician, while the other was undertaken in Taiwanese by the final-year medical student who had translated the letter of invitation. Translated paper versions of the questionnaire were used for these interviews and the responses of next of kin were entered into the computer later.

8.4.8 Estimation of the absolute risk of fatal pulmonary embolism following long-distance air travel

As already discussed, the cases who had undertaken long-distance air travel in the four weeks before the index date were identified through interviews with next of kin and by examining existing records. Statistics New Zealand provided records of the numbers of short-term arrivals on international flights by New Zealand residents and overseas visitors, by sex and five-year age groups, in the years 1990 to 2000. These data, derived from analyses of the arrival cards which all travellers arriving in New Zealand are required to complete, were used to calculate the number of arrivals on flights of at least three hours' duration. Because travellers are asked to record only the airport from which their last flight departed, these data provided insufficient information about the total duration of air travel undertaken by arriving passengers. Therefore, information from the control series in the case-control study was used to estimate the number of arrivals by New Zealand residents following air travel of more than eight hours during the same

period. The proportion of controls who arrived on a flight of more than eight hours in the four weeks before the index date was multiplied by 13 (to estimate the proportion over one year) and the product multiplied by the annual estimates of the New Zealand population aged 15 – 59 years to estimate the number of arrivals by New Zealand residents on flights of more than eight hours in the years 1990 to 2000. To assess the validity of this approach, the number of arrivals on international flights of any duration was estimated and compared with the arrivals data provided by Statistics New Zealand.

The absolute risks of dying from pulmonary embolism after a long-distance flight were estimated by dividing the number of cases who undertook a long-distance flight in the four weeks before the index date by the number of passengers aged 15 – 59 years who arrived in New Zealand between 1990 and 2000. For New Zealand residents and overseas visitors, the absolute risks of dying from pulmonary embolism following a flight of at least three hours' duration were calculated using the arrivals data supplied by Statistics New Zealand. For New Zealand residents only, the risks after a flight of at least three hours' duration and a flight of more than eight hours were calculated using the estimated numbers of arrivals derived from the control series. The Poisson distribution was used to compute 95% confidence intervals for the estimates of absolute risk.

8.4.9 Comparison of mortality rates in overseas visitors and New Zealand residents

Numbers of deaths from pulmonary embolism and from all causes

As already explained in Chapter 2, the New Zealand Health Information Service provided the details of 121 people aged 15 – 59 years who died from pulmonary embolism between 1990 and 2000. The numbers of deaths from all causes in New Zealand residents and overseas visitors by sex and five-year age groups for the years 1990 – 1998 were also obtained from the New Zealand Health Information Service. Data for 1999 and 2000 were not available for all-cause deaths because the country of usual residence was not coded in these years. Existing records were used to determine whether people who died from pulmonary embolism in 1999 and 2000 had been resident in New Zealand or overseas.

Sources of population data for New Zealand residents and overseas visitors

The estimated mean New Zealand resident population by sex and five-year age groups on 31 December in the years 1990 to 2000 was obtained from Statistics New Zealand. These estimates were based on the national Census of Population and Dwellings that is conducted by Statistics New Zealand quinquennially in the month of March. In census years the resident population is estimated by adding the number of residents who were present in New Zealand and counted on the census date to the number of residents who were temporarily overseas on that date, and then adjusting this figure for a net census undercount (Statistics New Zealand 2002). In non-census years, birth, death, and net migration data are used to update the estimates.

Census date counts of the overseas visitor population by sex and five-year age groups for the years 1986, 1991, 1996, and 2001 were also obtained from Statistics New Zealand. Sex and age-specific estimates for intervening years were derived by linear interpolation. For example, the difference between the March 1996 and 1991 census counts was multiplied by 0.2, 0.4, 0.6, and 0.8, and then added to the 1991 count to estimate the overseas visitor populations in March 1992, 1993, 1994, and 1995 respectively.

Because seasonal trends were evident in the monthly sex- and age-specific estimates of short-term overseas visitor arrivals between 1990 and 2000, the visitor census counts and estimated population in non-census years were seasonally adjusted. In brief, for each sex and five-year age stratum, the total number of arrivals in each year was divided by 12 to obtain the mean monthly arrivals for that year. To calculate the seasonal adjustment factor for each stratum for that year, the estimated visitor population for the month of March was divided by the mean monthly arrivals. The March population count or estimate was then divided by the correction factor to derive the seasonally-adjusted estimate.

Person-years of observation

Sex and age-specific population data for New Zealand residents and for overseas visitors were added together to calculate the person-years of observation in residents and visitors for the relevant periods. For the comparison of pulmonary embolism mortality in the overseas visitor and the New Zealand resident populations, person-years

for the period 1990 to 2000 were calculated. For deaths from all causes, the relevant period was 1990 to 1998.

Calculation of adjusted rate ratios and standardised mortality ratios

Direct and indirect methods of sex and age standardisation were used to compare mortality rates for pulmonary embolism and all causes in the overseas visitor population with the rates in the New Zealand resident population (Hennekens and Buring 1987). Both methods were used because of the potential for unstable estimates with small numbers. The Poisson distribution was used to compute 95% confidence intervals for the adjusted rate ratios and standardised mortality ratios.

8.4.10 Estimation of attributable proportion

To estimate the attributable proportion, it was assumed that the mortality rate from pulmonary embolism in the overseas visitor population approximated the rate in recent long-distance air travellers (mortality rate in the exposed) and the rate in the New Zealand resident population was similar to the rate in non-travellers (mortality rate in the unexposed). To calculate the proportion (percent) of deaths from pulmonary embolism among people who had recently undertaken a long-distance flight, which could be attributed to the flight itself, the mortality rate in the unexposed was subtracted from the mortality rate in the exposed, divided by the mortality rate in the exposed, and multiplied by 100 (Hennekens and Buring 1987). The first calculations were based on the mortality rate for overseas visitors which had been standardised to the sex and age distribution of the New Zealand resident population. However, because the sex and age distribution of the New Zealand residents who undertook long-distance air travel differed slightly from that of the general population, the attributable fraction was also calculated after standardising the mortality rates of both the overseas visitors and the resident population to the sex and age distribution of the New Zealand air travellers (using the arrivals data provided by Statistics New Zealand).

8.4.11 Ethical matters

Ethical approval for the research was granted by each of the 12 regional ethics committees that were in existence at the time the study was designed. Further

discussion of ethical matters relating to both the descriptive study and the case-control study can be found in Chapter 10.

CHAPTER 9 DESCRIPTIVE STUDY OF LONG-DISTANCE AIR TRAVEL: RESULTS AND DISCUSSION

9.1 RESULTS

9.1.1 Participation of next of kin

As described in the previous chapter, one of the cases who was a New Zealand resident had no identified next of kin and the husbands of two overseas cases were not traced. Hence, there were 118 cases for whom the contact details of next of kin were available. Figure 9.1 shows the responses of these next of kin to the letters that invited them to take part in the study. For 103 of the 118 cases, letters were sent to just one relative. For the remaining 15 cases it was necessary to write to more than one relative because the letters sent to the first next of kin were either returned by the postal service ("gone, no forwarding address"), or no response was received and the next of kin did not have a traceable telephone number; for eight cases a second next of kin was sent at least one letter, for six cases three next of kin were sent letters, and for one case letters were sent to a total of six next of kin.

The next of kin of 103 (85.1%) of the 121 cases eligible for inclusion in the descriptive study were interviewed. Only eight (6.6%) next of kin directly declined to participate (five husbands, one wife, and two mothers). The sons of two women consented to an interview, but both subsequently proved to be impossible to contact. The other next of kin of these two cases (the husband and a son of one, and the husband and four daughters of the other) did not reply to letters of invitation. For five cases, none of the identified next of kin had traceable telephone numbers, and despite sending several letters in turn to each relative, no replies were received.

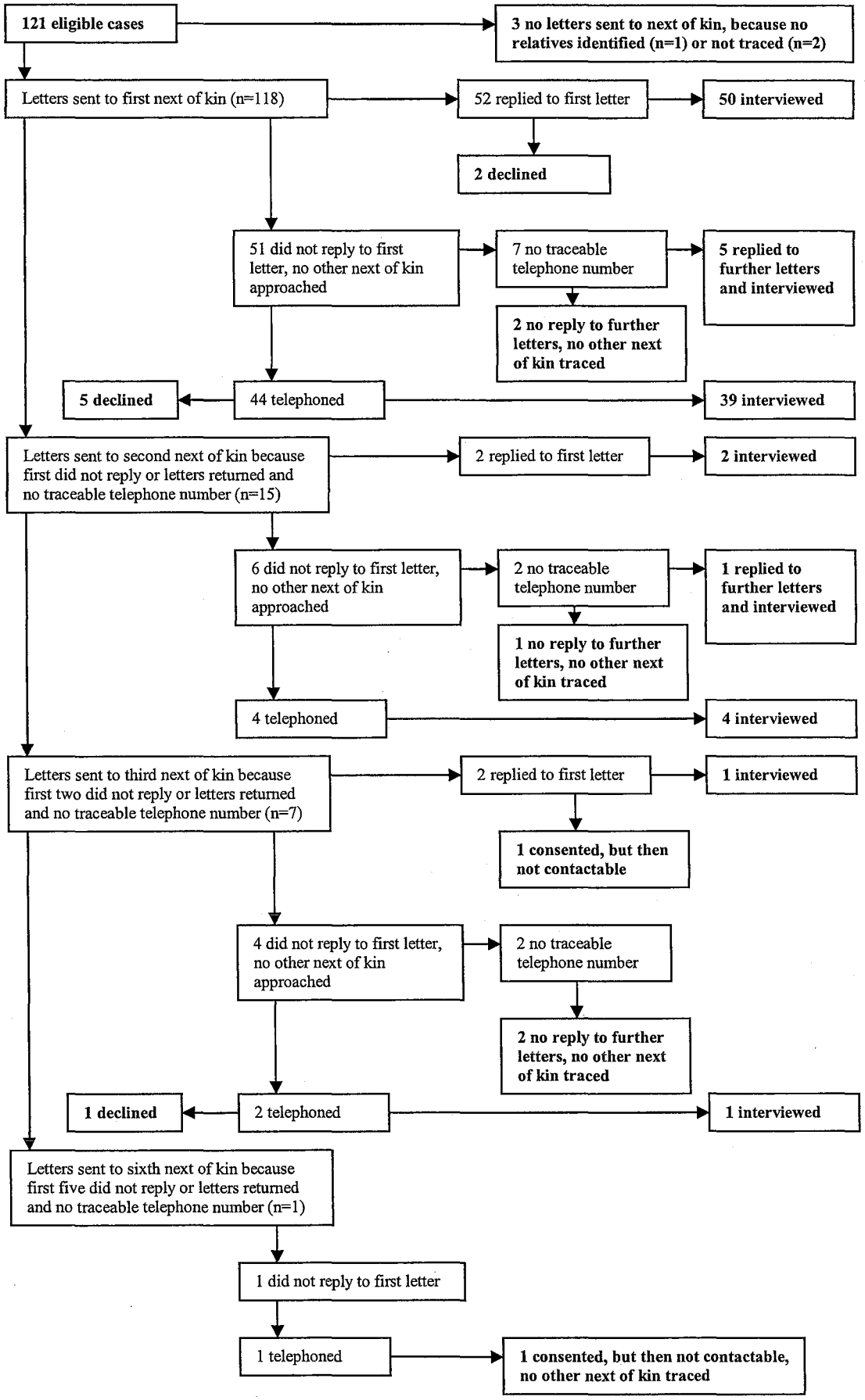

Figure 9.1 Participation of next of kin

Fifty-four of the 103 next of kin interviews were conducted with the spouse, de-facto partner, or adult family member with whom the case had lived on the index date (Table 9.1). Another 17 cases were known to have lived with a spouse, partner, or family member on the index date, but a different relative was interviewed (Table 9.2). The reasons for this were varied: the husbands of three cases had died, six spouses and two adult children were not traced, one spouse and two partners did not respond to the letters of invitation, one partner's name was unknown, one case lived with an uncle but it was felt more appropriate to interview his father, and the husband of one case declined to participate but her father volunteered when he was being interviewed about his wife who was also a case.

Of the remaining 32 cases, existing records indicated that four lived with young children, three with flatmates or boarders, two lived in psychiatric half-way houses, six were intellectually disabled and lived in supported accommodation, 12 lived alone, and the living circumstances of five were not documented (Table 9.1). For each of these cases, the closest named relative was interviewed.

Table 9.1 Next of kin who were interviewed and their relationship to the case

Persons with whom the case had lived on the index date*	Next of kin interviewed (n=103)	New Zealand residents	Overseas visitors
Husband / male partner (n=37)	Husband / male partner	24	-
	Husband and daughter	1	-
	Husband and brother-in-law	1	-
	Mother	2	-
	Father and uncle	1	-
	Father	-	1
	Daughter or son	6	-
	Sister-in-law	-	1
Wife / female partner (n=22)	Wife / female partner	18	1
	Mother and brother	1	-
	Brother	1	-
	Cousin	-	1
Both parents (n=3)	Mother	3	-
Mother (n=5)	Mother	4	-
	Mother and aunt	1	-
Sister (n=1)	Sister	1	-
Adult son (n=1)	Another son	1	-
Adult daughter (n=1)	Sister	1	-
Uncle (n=1)	Father and sister	1	-
Young children only (n=4)	Mother	3	-
	Ex-husband	1	-
Flatmates or boarder (n=3)	Mother	1	-
	Ex-husband	1	-
	Sister-in-law	1	-
Psychiatric half-way house (n=2)	Brother	1	-
	Son	1	-
Intellectually disabled care (n=6)	Mother	2	-
	Sister or brother	4	-
Lived alone (n=12)	Mother	2	-
	Sister	3	-
	Daughter or son	2	-
	Cousin	1	-
	Friends	4	-
Unknown (n=5)	Parents	1	-
	Mother	1	-
	Sister or brother	2	-
	Brother and friends	-	1
Total		**98**	**5**

* According to Notification of Death for Registration forms, coroners', hospital, and other existing records.

Table 9.2 Reasons why next of kin other than those with whom the cases had lived were interviewed

Next of kin with whom the case had lived on index date*	Reason why next of kin with whom the case had lived was not interviewed	Next of kin who was interviewed
Husband / male partner (n=11)	Husband died after index date	Son
	Husband died after index date	Daughter
	Husband died after index date	Sister-in-law
	Name of partner unknown	Mother
	Husband not traced	Mother
	Husband not traced	Father
	Husband not traced	Son
	Husband not traced	Daughter
	Husband declined, father volunteered when he was contacted about his wife who was also a case	Father and uncle
	Husband did not reply to letters of invitation	Son
	Partner did not reply to letters of invitation	Son
Wife / female partner (n=3)	Wife not traced	Mother and brother
	Wife not traced	Cousin
	Partner did not reply to letters of invitation	Brother
Son (n=1)	Two sons did not reply to letters of invitation	Another son
Daughter (n=1)	Daughter not traced	Sister
Uncle (n=1)	Father thought to be more appropriate	Father and sister

* According to Notification of Death for Registration forms, coroners', hospital, and other existing records.

9.1.2 Long-distance air travel

The next of kin of nine cases reported that their relative had undertaken at least one international flight in the four weeks before the index date. These flights were all confirmed by medical and death records. Of the 18 cases for whom next of kin interviews were not undertaken, two were identified as international air travellers — long-distance flights to New Zealand were documented in the coroner's records of one of these women and the hospital records of the other (a doctor-certified death). Both were overseas visitors whose husbands were not traced. The existing records of the remaining 16 cases (15 residents and one overseas visitor who was known to have been in New Zealand for more than a month), contained no references to long-distance air travel before the index date. Table 9.3 shows which records were examined for these cases.

Table 9.3 Existing records examined for cases whose next of kin were not interviewed in which there was no mention of long-distance air travel

Existing records examined	Number of cases
General practitioners', hospital, and coroners' records	3
General practitioners' and coroners' records	6
General practitioner's, coroner's, and family planning records	1
General practitioner's, coroner's, and mental health records	1
General practitioners' and hospital records	2
Hospital and coroner's records (overseas visitor)	1
Hospital, coroner's and mental health records	1
Coroner's records	1
Total	**16**

Although a further two cases were found to have undertaken return three to four hour flights to the east coast of Australia about two and three weeks before they died (the next of kin of one was interviewed, the other was identified using existing records), these journeys were undertaken after the index date: a 33 year old woman was being treated for deep vein thrombosis and a 58 year old man had already developed symptoms of pulmonary embolism and at necropsy was found to have pulmonary emboli of varying ages.

There were no additional subjects who had undertaken domestic flights within a country other than New Zealand during the relevant period. Thus, 11 (9.1%) of the 121 cases (five New Zealand residents and six overseas visitors) were determined to have undertaken long-distance air travel in the four weeks before the index date. The characteristics of these people are shown in Table 9.4. Seven were female and four were male. The median age was 47.9 years. Several of these cases had other risk factors for venous thromboembolism. Two people had a personal, as well as a family, history of deep vein thrombosis. One developed deep vein thrombosis during her sixth and final full-term pregnancy, 13 years before the onset of the fatal episode. She subsequently suffered from post-thrombotic syndrome, but her symptoms were relieved by surgery to her varicose veins six years before her death. An uncle and three of her cousins had been diagnosed with deep vein thrombosis. Following her death, three of her six children were found to have protein S deficiency. The other case developed deep vein thrombosis following a bicycling accident ten months before the index date and was treated with a six-month course of warfarin. One of his aunts also had a history of deep vein thrombosis. Another two cases had taken medications which are associated with an increased risk of venous thromboembolism: one was receiving hormone replacement therapy and the other had taken norethisterone, medroxyprogesterone acetate, and tranexamic acid to treat menorrhagia. A fifth case had become paraplegic following a fall 33 years earlier and was using continuous ambulatory peritoneal dialysis for chronic renal failure. He and four other cases had a BMI greater than 30 kg/m^2.

Table 9.4 Characteristics of cases who undertook long-distance air travel in the four weeks before the index date

Case*	Sex	Age (years)	Past venous thromboembolism	BMI (kg/m^2) †	Other risk factors for venous thromboembolism‡	Family history of venous thromboembolism
1	Female	47	No	34.9	Norethisterone Medroxyprogesterone acetate Tranexamic acid	No
2	Female	51	Pregnancy-related deep vein thrombosis	"tall, rather obese" ("average")	History of varicose veins	1 uncle, 3 cousins
3	Female	58	No	21.6	History of varicose veins Hormone replacement therapy	No
4	Male	36	No	31.2	Nil	No
5	Male	49	No	34.3	Paraplegia 33 years	No
6	Female	42	No	"well-built" (26.1)	Nil	No
7	Female	47	No	43.6	Nil	No
8	Female	54	Unknown	Unknown	Unknown	Unknown
9	Female	57	Unknown	30.4	Nil reported to airport medics	Unknown
10	Male	32	Injury-related deep vein thrombosis	"well-nourished" (28.9)	Nil	1 aunt
11	Male	39	No	24.2	Nil	No

* Cases 1 – 5 were usually resident in New Zealand on the index date, cases 6 – 11 were overseas visitors. Information about cases 8 and 9 was obtained from coroners' and hospital records only, as next of kin were not traced.

† Pathologists' comments and BMI calculated from weight and height at necropsy. Next of kin comments and BMI calculated from reported weight and height are shown in parentheses.

‡ Information was sought about major risk factors for venous thromboembolism in the three months before the index date (including surgery, major injury, prolonged immobility, pregnancy, hospital admissions for other reasons, hormone replacement therapy, and the use of oral contraceptives, psychotropic drugs and other medications), varicose veins, known thrombophilia, systemic lupus erythematosus, inflammatory bowel disease, other medical conditions, ethnicity, and smoking.

Table 9.5 shows the details of the long-distance flights undertaken by the 11 cases in the four weeks before the index date. One case had undertaken three long-distance journeys during the relevant period, and two had flown on two separate occasions. The remaining cases flew only once in the four weeks before the index date, although two women each undertook a further flight after the onset of their fatal episode.

One of these women (Case 2) developed severe right sided chest and upper abdominal pain seven days after flying from Christchurch to Western Australia (total flight time of eight hours five minutes). At this time she consulted a general practitioner who attributed her symptoms to "a viral infection" and prescribed an analgesic. Following her return to New Zealand seven days later, she experienced intermittent chest pain from the evening of her arrival until two days later when she collapsed and died at home. Necropsy findings included fresh embolus completely occluding the left and right main pulmonary arteries, older emboli in the peripheral vessels, small fresh (one to two days' old) infarcts in both lungs, and an older (one to two weeks' old) infarct in the right lower lobe.

The second woman (Case 3) complained of unilateral calf pain and shortness of breath on arrival at Singapore, following a flight from London (non-stop flight of 12 hours 45 minutes). An airport medical practitioner suspected pulmonary embolism and sent her by ambulance to a local hospital, where she spent several hours. No apparent cause was found for her symptoms and she spent the next three days resting at a hotel before flying from Singapore to Auckland. She required oxygen during this flight. On arrival in New Zealand she undertook a short domestic flight without difficulty. The following morning she collapsed and was transported to the local hospital's emergency department where she died. At necropsy, the main pulmonary arteries were completely occluded by fresh embolus and thrombi were found in the deep veins of the right calf. No older pulmonary emboli or infarcts were seen.

Nine (five New Zealand residents and four overseas visitors) of the 11 air travellers had journeys of at least eight hours. Seven travelled in economy class, one had undertaken two flights in economy class and one in business class, and for three cases the class of travel was not determined. None were reported to have taken hypnotic drugs immediately before or during the flight. One woman had travelled for five hours by bus

directly before a flight and one man undertook several bus trips during the four-week period.

For nine people (five New Zealand residents and four overseas visitors), the symptoms of venous thromboembolism developed within eight days of a flight. Four cases, including Case 3 who has already been discussed, developed symptoms during or immediately after a long-distance flight. Case 1 became dizzy and short of breath on a flight from Bangkok to Auckland (total flight time of 11 hours 45 minutes). On arrival at Auckland International Airport she had an episode of vomiting and diarrhoea, and collapsed. She was reportedly assessed by airport staff and sent home. A few hours later she was admitted to hospital with increasing shortness of breath, but collapsed and died. Emboli were found throughout the major and minor pulmonary arteries. Case 8 complained of abdominal pain and distension one hour before landing at Auckland after a flight from Japan (total flight time of 11 hours). She collapsed soon after disembarking but was resuscitated and transferred to the nearest hospital's intensive care unit. A computerised tomography pulmonary angiogram confirmed the presence of multiple large pulmonary emboli. She was given thrombolytic therapy and supportive care, but was later pronounced brain dead. Case 9 complained of feeling hot and unwell on the first leg of her journey from London to Auckland (total flight time of 22 hours 50 minutes), but there was no record of her having sought medical attention during a two hour wait at Singapore Airport. She collapsed and died at Auckland International Airport. Fresh emboli were found throughout the pulmonary vasculature at necropsy.

Only two of the air travellers were admitted and died in hospital, two others died on arrival at hospital emergency departments, one died while visiting a relative in hospital, and six died at home or elsewhere in the community.

Table 9.5 Long-distance air travel undertaken by cases in the four weeks before the index date

Case*	Next of kin interviewed	Number of long-distance journeys undertaken by air	Total duration of long-distance journey (duration of each leg)	Number of stops during journey (duration)	Class of travel	Aisle seat	Hypnotic use	Interval between flight and onset of symptoms	Journeys of at least four hours by other modes of transport
1	Daughter	2	13 h, 25 m (11 h 5 m, 2 h 20 m)	1 (unknown)	Economy	Unknown	No	14 days	5-hour bus trip before 2nd journey
			11 h, 45 m (8 h 50 m, 2 h 55 m)	1 (1 h)	Economy	Unknown	No	During flight	
2	Husband	1	8 h, 5 m (3 h 15 m, 4 h 50 m†)	1 (1 – 2 h)	Economy	Unknown	No	7 days	Unknown
3	Husband	1	12 h, 45 m	0	Economy	Yes	No	On disembarking	No
4	Brother	3	9 h, 20 m	0	Economy	Unknown	Unknown	24 days	No
			10 h, 30 m	0	Economy	Unknown	Unknown	9 days	
			9 h, 20 m	0	Business	Unknown	Unknown	4 days	
5	Wife	2	12 h, 0 m	0	Economy	Yes	No	7 days	No
			12 h, 0 m	0	Economy	Yes	No	2 days	
6	Father	1	3 h, 30 m	0	Economy	Unknown	Unknown	8 days	Possibly

Case*	Next of kin interviewed	Number of long-distance journeys undertaken by air	Total duration of long-distance journey (duration of each leg)	Number (duration) of stops during journey	Class of travel	Aisle seat	Hypnotic use	Interval between flight and onset of symptoms	Journeys of at least four hours by other modes of transport
7	Sister-in-law	1	3 h, 0 m	0	Unknown	Unknown	Unknown	24 days	No
8	Not traced	1	11 h, 0 m	0	Unknown	Unknown	Unknown	During flight	Unknown
9	Not traced	1	22 h, 50 m (12 h 45 m, 10 h 5 m)	1 (2 h)	Unknown	Unknown	No	During first leg of journey	Unknown
10	Brother	1	4 h, 15 m	0	Economy	Unknown	No	25 days	Probably
11	Cousin	1	11 h, 0 m	0	Economy	Unknown	No	2 days	No

* Cases 1 – 5 were usually resident in New Zealand on the index date, cases 6 – 11 were overseas visitors.
† Domestic flight within a country other than New Zealand.

Abbreviations used in the table h: hours, m: minutes

9.1.3 Long-distance travel by other modes of transport

A further 11 cases, who had not undertaken long-distance air travel, undertook at least one car journey of more than four hours' duration in the four weeks before the index date and one made several trips in a small boat (Table 9.6). It was not possible to estimate the absolute risks of fatal pulmonary embolism for these modes of transport because of the lack of denominator data.

Table 9.6 Long-distance travel by other modes of transport in the four weeks before the index date by cases who did not undertake long-distance air travel

Sex	Age (years)	Mode of transport	Total duration of journey(s)	Interval between journey(s) and onset of symptoms
Female	26	Car	6 h 50 m	2 days
Female	29	Car*	14 h 0 m	Immediate onset
Female	34	Car Car	5 h 50 m 5 h 50 m	Unknown Unknown
Female	45	Car	5 h 0 m	Immediate onset
Female	53	Car Car	4 h 20 m 4 h 20 m	23 days 21 days
Female	58	Car	4 h 30 m	Unknown
Male	43	Car	4 h 15 m	21 days
Male	52	Bus driver Car	8 h 0 m 7 h 40 m	6 – 28 days 5 days
Male	55	Car Car Car Car	4 h 50 m 5 h 10 m 5 h 10 m 4 h 50 m	12 days 10 days 4 days 3 days
Male	55	Small boat	6 – 8 h	Unknown (4 or 5 trips during 4 weeks before index date)
Male	56	Taxi driver	12 h 0 m	1 – 28 days
Male	58	Car Car	6 h 5 m 6 h 5 m	26 days 15 days

* Psychiatrically unwell and sat in car overnight.

9.1.4 Absolute risk of fatal pulmonary embolism following a long-distance flight

The risks of developing fatal pulmonary embolism in the four weeks following a long-distance flight are shown in Table 9.7. Using Statistics New Zealand migration data as the denominator, the risks following a flight of at least three hours' duration were 0.5 (95% CI 0.2 – 1.2) and 0.6 (95% CI 0.2 – 1.4) per million arrivals for overseas visitors and New Zealand residents respectively. Using arrival estimates based on exposure data from controls in the case-control study as the denominator, the risk in residents following a flight of more than eight hours' duration was 1.3 (95% CI 0.4 – 3.0) per million arrivals, while the risk following a flight of at least three hours' duration was identical to that obtained using Statistics New Zealand migration data.

Table 9.7 Absolute risk of dying from pulmonary embolism following long-distance air travel

	Number of deaths among international arrivals aged 15 – 59 years, 1990 – 2000	**Number of international arrivals aged 15 – 59 years, 1990 – 2000**	**Absolute risk per million international arrivals (95% CI)**
Overseas visitors, air travel ≥ 3 hours' duration	6	11,224,909*	0.5 (0.2 – 1.2)
New Zealand residents, air travel ≥ 3 hours' duration	5	8,100, 951*	0.6 (0.2 – 1.4)
New Zealand residents, air travel ≥ 3 hours' duration	5	8,675,292†	0.6 (0.2 – 1.3)
New Zealand residents, air travel > 8 hours' duration	5	3,855,960†	1.3 (0.4 – 3.0)

*Number of arrivals provided by Statistics New Zealand.
†Estimated number of arrivals based on data from the case-control study.

9.1.5 Pulmonary embolism and all-cause mortality rates

The mortality rate from pulmonary embolism in the overseas visitor population was higher than the rate in the New Zealand resident population (Table 9.8); the sex and age-adjusted rate per million person-years in the overseas visitor population was 19.70 compared with 4.56 in the New Zealand resident population. The adjusted mortality rate ratio was thus 4.3 (95% CI 3.9 – 4.7); the standardised mortality ratio was 3.8 (95% CI 1.6 – 7.4). This is consistent with an increased risk of pulmonary embolism in air travellers, since almost all overseas visitors arrive by air and about 90% of visitors remain in New Zealand for less than 30 days (Statistics New Zealand 2001a), while only a small proportion of the resident population undertakes international air travel during a four-week period.

These results are particularly striking, given that there appears to be a "healthy traveller" effect. During the period 1 January 1990 to 31 December 1998 there were a total of 40,471 deaths from all causes in New Zealand residents and 533 in overseas visitors aged 15 – 59 years. The sex and age-adjusted mortality rates for all causes per million person-years were 1465.83 and 2022.42 in the overseas visitor and New Zealand resident populations respectively (Table 9.8). Hence, the adjusted mortality rate ratio was 0.72 (95% CI 0.71 – 0.73). The standardised mortality ratio was 0.71 (95% CI 0.64 – 0.76).

Table 9.8 Mortality from pulmonary embolism and all causes in the overseas visitor and New Zealand resident populations

Cause of death	Mortality rate in overseas visitor population* (per million person-years)	Mortality rate in New Zealand resident population (per million person-years)	Adjusted rate ratio (95% CI)
Pulmonary embolism	19.70	4.56	4.32 (3.94 – 4.72)
All causes	1465.83	2022.42	0.72 (0.71 – 0.73)

* Standardised to the sex and age distribution of the New Zealand resident population.

9.1.6 Attributable proportion

Based on the assumptions that the mortality rate from pulmonary embolism in the overseas visitor population approximates the rate in recent air travellers, and that the rate in the New Zealand resident population is similar to the rate in non-travellers, the proportion of deaths from pulmonary embolism in people who had recently undertaken long-distance air travel which could be attributed to the flight itself was estimated using the following formula (Hennekens and Buring 1987):

$$\text{Attributable proportion} = \frac{I_e - I_o}{I_e} \times 100$$

Where I_e = sex and age-adjusted mortality rate from pulmonary embolism in overseas visitors

and I_o = mortality rate from pulmonary embolism in New Zealand residents

Thus, it was estimated that 76.8% of deaths from pulmonary embolism in people who had recently undertaken a long-distance flight could be attributed to the flight itself. In this estimation, the mortality rate for overseas visitors was standardised to the sex and age distribution of the New Zealand population aged 15 – 59 years. However the age distribution of New Zealand men aged 15 – 59 years who undertook long-distance air travel between 1990 and 2000 differed from those who did not — about 34% of the air travellers were aged between 35 – 59 years as compared with 25% of the total population of New Zealand. No such difference was observed for women. Because the age structure of male travellers differed from the general population, the attributable fraction was recalculated after standardising the mortality rates for the overseas visitor and New Zealand resident populations to the sex and age distribution of the New Zealand air travellers (using arrivals data provided by Statistics New Zealand). While the mortality rates in overseas visitors and New Zealand residents increased slightly (to 22.72 and 5.18 per million person-years respectively), the attributable fraction barely changed (77.2%).

9.2 DISCUSSION

In this study of 121 men and women aged 15 – 59 years who died from pulmonary embolism in New Zealand between 1990 and 2000, 11 (9.1%) of the cases had

undertaken long-distance air travel in the four weeks before the onset of the fatal episode. Long-distance air travellers appeared to have a higher risk of fatal pulmonary embolism than non-travellers; the mortality rate from pulmonary embolism in the overseas visitor population (most of whom would recently have undertaken long-distance flights) was about four times higher than the rate in the resident population of New Zealand. Conversely, the mortality rate from all causes in overseas visitors was about 30% lower than the rate in New Zealand residents. Allowing for this "healthy traveller" effect, air travel may carry as much as a six-fold increase in risk. In absolute terms, however, the risk of dying from pulmonary embolism after a long-distance flight appears to be very low. The absolute risks in people aged 15 – 59 years following a flight of at least three hours' duration were 0.5 (95% CI 0.2 – 1.2) and 0.6 (95% CI 0.2 – 1.4) per million arrivals for overseas visitors and New Zealand residents respectively. The risk in New Zealand residents following a flight of more than eight hours was 1.3 (95% CI 0.4 – 3.0) per million arrivals.

9.2.1 Strengths and limitations of the research

One of the strengths of this population-based research, as outlined in the discussion in Chapter 6, is that the ascertainment of eligible cases who died in New Zealand during the study period is likely to have been complete. Any air travellers who died on a flight en-route to New Zealand would also have been identified in this study, except in rare situations where the aircraft did not proceed as intended.

As the study included deaths that occurred between 1990 and 2000, some next of kin were required to recall whether their relative had undertaken a long-distance flight during a four-week period more than 10 years earlier. Wherever possible, the next of kin with whom the cases had lived on the index date were interviewed. These people appeared to be a reliable source of information, as all long-distance flights reported by next of kin were confirmed by medical and death records. Similarly, existing records did not identify any flights that were not also reported by next of kin. It was not possible to interview all next of kin, but existing records identified only two further air travellers, both of whom were overseas visitors whose next of kin were not traced.

The estimates of absolute risk in this study are based on a group of 15 – 59 year old men and women, for whom cancer, other medical conditions, or pregnancy were not

considered to be the underlying cause of death. It was not possible to exclude people with these conditions from the arrivals data, but it is unlikely that there would have been sufficient numbers to have substantially biased the estimates of absolute risk. Moreover any such bias would be in a conservative direction and result in an underestimate of the mortality rate.

Because of the way in which mortality data were recorded during the study period, it was not possible to identify all people for whom pulmonary embolism was the mechanism, but not the underlying cause, of death. Hence, it was not possible to estimate flight-related mortality rates in groups with predisposing conditions, in whom the absolute risk of fatal pulmonary embolism following a long-distance flight is likely to be greater. Nevertheless, the cases studied were not an entirely idiopathic group, since people with a personal history of venous thromboembolism, recent hospital admission, major injury, prolonged immobilisation, and obesity, as well as users of oral contraceptives, hormone replacement therapy, and antipsychotics, were included.

It was not possible to ascertain the duration of air travel from the migration data provided by Statistics New Zealand, but the use of information from the control series (in the accompanying case-control study) to estimate the risk of fatal pulmonary embolism in people who undertook air travel of more than eight hours' duration appears to have been a reasonable approach — identical estimates of risk were obtained for flights of at least three hours' duration using information from the control series and the official migration data. Because deaths in which fatal pulmonary embolism is the underlying cause are rare, a more detailed exploration of risk by duration of travel was not possible owing to the inevitably small number of flight-related deaths.

Denominator data for long-distance flights within countries other than New Zealand were not available. However the only case who undertook domestic flights within a country other than New Zealand, undertook these flights immediately after and before her international flights from and to New Zealand. Hence, these domestic flights were considered in conjunction with her international flights.

9.2.2 Consistency with previous research

Nine percent of cases in the present study had undertaken long-distance air travel in the four weeks before the onset of the fatal episode. This accords with the results of a later New Zealand records-based study, in which 10.4% of patients who were admitted to four hospitals with confirmed venous thromboembolism had a documented history of air travel within 28 days of admission (Hughes et al. 2006). The only other studies to have determined the proportion of air travellers among a series of cases with venous thromboembolism were based on non-fatal events and the results are inconsistent. In a study of 182 consecutive patients admitted to hospitals in Glasgow with pulmonary embolism over a three-year period, only three (1.6%) were reported to have undertaken long-distance air travel shortly before the onset of symptoms (Symington and Stack 1977). It is not clear, however, whether all the patients were questioned about travel, so this could represent an underestimate. Similarly a review of medical records in a Western Australian hospital found that, of 250 patients admitted with venous thromboembolism during a three-year period, only eight (3.2%) had a documented history of "recent" (not defined) long-distance flights (O'Donnell 1988). In a population-based study undertaken in the north of England, 1,250 consecutive patients admitted to hospital over a two-year period with objective evidence of venous thromboembolism were asked about risk factors using an interviewer-administered questionnaire (Kesteven and Robinson 2002). Twenty-eight (2.2%) reported undertaking a flight (unspecified) in the four weeks before diagnosis. By contrast, in two Hawaiian case series based on retrospective review of hospital records, 17% (Eklof et al. 1996) and 25% (Mercer and Brown 1998) of the cases had undertaken flights of at least five hours up to six weeks before the onset of symptoms. In a subsequent Hawaiian study, 25 of 109 patients (23%) admitted between July 1995 and October 1998 with objective evidence of venous thromboembolism gave a history of recent air travel when interviewed in hospital (Arfvidsson et al. 1999).

It is not possible to make meaningful comparisons between these studies and the present research for several reasons. In the absence of control groups it is impossible to know whether the underlying frequency of long-distance air travel in the source population differed between studies and, indeed, whether the proportion of cases exposed to recent air travel was any higher than would be expected in the source population. If crude numbers are examined, there were certainly more international arrivals in Hawaii

annually between 1988 and 1993 (Eklof et al. 1996), than there were in New Zealand in 1990 (six million c.f. 1.7 million).

The Hawaiian studies also included people over the age of 59 years and a substantial proportion of the cases had malignancies or had recently undergone surgery (as well as having other risk factors for venous thromboembolism). Given the multi-causal nature of venous thromboembolism, a long-distance flight in people who had several pre-existing risk factors might have been enough to trigger a thromboembolic event. Hence, it is perhaps not surprising that higher proportions of air travellers were found in the studies which included people with multiple risk factors for venous thromboembolism.

The observation that several other cases in the present study had undertaken long journeys by car and other modes of transport is consistent with previous case reports (Homans 1954; Symington and Stack 1977; Voorhoeve and Bruyninckx 1990; Benoit 1992; Schmitt and Mihatsch 1992; Tardy et al. 1993; Eschwège and Robert 1996; Nissen 1997; Parsi and McGrath 2000; Parsi et al. 2001; Partsch 2001; Kesteven and Robinson 2002; Tan et al. 2002; Bertos-Polo et al. 2003; McQuillan et al. 2003; Lapostolle et al. 2004; Hitosugi et al. 2005).

The finding in the present study that long-distance air travellers had a higher risk of fatal pulmonary embolism than non-travellers is consistent with some (Ferrari et al. 1999; Arya and Cohen 2003; Martinelli et al. 2003; Schwarz et al. 2003; Becker et al. 2006; Cannegieter et al. 2006), but not all (Kraaijenhagen et al. 2000; Hosoi et al. 2002; ten Wolde et al. 2003), previous analytical studies of non-fatal events. This will be discussed in greater detail in Chapter 11.

Assuming a case-fatality rate of 2 – 5% (Cushman et al. 2004; Goldhaber 2004), the estimates of pulmonary embolism mortality in the present study are higher than would be expected based on studies of non-fatal cases referred to hospitals located near airports (Clerel and Caillard 1999; Lapostolle et al. 2001; Hertzberg et al. 2003; Perez-Rodriguez et al. 2003), presumably because it was possible to include all cases that occurred in New Zealand in the days following a long-distance flight. In contrast, the present estimates are much lower than would be expected from studies of volunteers who developed asymptomatic venous thromboembolism (Arfvidsson et al. 1999;

Belcaro et al. 2001; Scurr et al. 2001; Belcaro et al. 2002; Cesarone et al. 2002; Belcaro et al. 2003; Schwarz et al. 2003; Cesarone et al. 2003c; Cesarone et al. 2003d) and from a study in which 1% of volunteers developed symptomatic non-fatal venous thromboembolism after a flight of at least 10 hours (Hughes et al. 2003). The clinical relevance of asymptomatic venous thromboembolism is unclear, and the latter study included subjects up to the age of 70 years and may have included a non-representative group of air travellers. For example, the mean age of the participants was 49 years and 51% were female, whereas in migration data provided by Statistics New Zealand the median age of New Zealand residents arriving back in the country between 1990 and 2000 after an absence of less than one year lay in the 40 – 44 year age group and 48% were female. Moreover venous thromboembolic events which occurred up to three months following a long-distance flight were defined as flight-related in the that study. The estimates of pulmonary embolism mortality in New Zealand residents and in overseas visitors following air travel of at least three hours' duration are consistent with the estimate of 0.5 deaths per million arrivals reported in the Western Australian record linkage study (Kelman et al. 2003), although the study groups were not strictly comparable. Indeed some features would have decreased their calculated risk and other features increased it, compared with the study described here.

The finding in this study that the rate of fatal pulmonary embolism was higher for flights of more than eight hours' duration, than for flights of three or more hours, is suggestive of a dose-response relationship — although it should be emphasised that these categories are overlapping. A dose-response relationship between duration of travel and risk of venous thromboembolism has been reported in previous studies (Lapostolle et al. 2001; Hertzberg et al. 2003).

9.3 SUMMARY AND IMPLICATIONS

These are presented in the final chapter, Chapter 12.

CHAPTER 10 CASE-CONTROL STUDY OF LONG-DISTANCE AIR TRAVEL: OBJECTIVE AND METHODS

10.1 OBJECTIVE

The objective of this case-control study was to examine any association between long-distance air travel in the four weeks before the index date and the risk of dying from pulmonary embolism. As outlined in Chapter 8, long-distance air travel was defined as a flight of at least three hours' duration and the date of onset of the fatal episode was taken as an index date. The four-week period was chosen to allow comparisons with the analytical studies that had been published at the time the study was initiated (Ferrari et al. 1999; Kraaijenhagen et al. 2000; Samama and the Sirius Study Group 2000; Arya et al. 2002; Martinelli et al. 2003).

10.2 METHODS

10.2.1 Ascertainment of cases

The methods used to identify all men and women aged 15 – 59 years who died in New Zealand between 1 January 1990 and 31 December 2000, for whom the underlying cause of death was pulmonary embolism, were described in Chapter 2. This case-control study was based on a subset of the 121 cases thus identified. The eight overseas visitors were excluded, as it was not possible to identify and contact members of an appropriate comparison group. Because controls were to be selected from the electoral roll, 14 cases who were New Zealand residents but were not registered on the electoral roll on the index date were also excluded. Thus, 99 cases were considered eligible for inclusion in the case-control study. The diagnosis of pulmonary embolism was confirmed by necropsy in 92, by pulmonary angiography or ventilation-perfusion scans in three, and by two physicians using standard criteria (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1995a) and blinded to exposure status in the remaining four cases.

10.2.2 Selection of controls

For each eligible case, four controls matched by sex, individual year of age, and electorate were selected randomly from electronic copies of the electoral roll. During the planning phase of the study, consideration was given as to whether the most recent electoral roll, or rolls from earlier years, should be used to select the controls. The advantage of using the most recent roll was that it would have been relatively simple to trace those who were selected. On the other hand, this approach would have precluded the selection of some potentially eligible controls such as those who had died after the index date and those who were not enrolled for some other reason. Hence, it was decided to use the electronic rolls from earlier years to select the controls. For cases whose index dates occurred between 1 January 1990 and 13 October 1994 (the date on which the 1994 paper electoral roll was compiled), the 1993 electronic roll was used to select potential controls; for index dates between 13 October 1994 and 31 December 1997 (no paper electoral roll was compiled in 1997), the 1996 electronic roll was used; for index dates between 1 January 1998 (the date on which the 1998 electronic roll was compiled) and 26 October 1999 (the date on which the 1999 paper roll was compiled), the 1998 electronic roll was used; and for index dates between 27 October 1999 and 31 December 2000, the 2000 electronic roll was used. For each case whose index date did not occur in 1993, 1996, 1998, or 2000, a paper copy of the roll from the index year was then examined to establish whether the people selected as potential controls for that case were enrolled in the appropriate electorate on the index date. Those who were not enrolled were excluded from the study.

Controls were matched to cases by electorate because regional differences in exposure to international travel have been observed in New Zealand (data provided by the New Zealand Blood Service). This process was complicated by the fact that population growth and electoral reform had led to changes in the number of electorates (and their boundaries) during the 11-year study period. Electoral boundaries are reviewed regularly in light of population estimates derived from the quinquennial Census of Population and Dwellings, with any changes coming into effect at the end of the three-year parliamentary term in which the changes were finalised (Statistics New Zealand 1998). These changes meant that for several of the cases (a subset of those whose index dates did not occur in the years in which the electronic rolls were compiled) the boundaries of the electorate to which they had belonged on the index date had changed

by the time the relevant electronic roll was compiled. For these cases, potential controls were selected from the electorate to which the case would have belonged on the date that the electronic roll was compiled.

To be eligible for inclusion in the study, selected persons had to be the same sex as the case, to have been born in the same year as the case, to have been normally resident in New Zealand on the index date, and to have been registered on the electoral roll in the same electorate as the case on the index date. People who did not meet the eligibility criteria, could not be traced, or did not consent to be interviewed were replaced.

Potential controls who did not wish to participate were asked if they were willing to answer two questions to establish eligibility. Those who agreed were asked for their date of birth and whether they were usually resident in New Zealand on the index date. Eligible participants and non-participants were also asked whether they were in New Zealand or overseas on the date of death of their case. This information was important to obtain because the exposure of interest, international travel, was clearly related to whether a potential control belonged to the population that gave rise to the case. In theory this population comprised otherwise eligible people who were in New Zealand on the date the case died, since to become a case, a person had to have died in New Zealand. However some cases died on their index date, while others did not. Thus, if potential controls who were not in New Zealand on the date of death of their case were excluded, some people who were overseas on the index date might also have been excluded. This, in turn, could have resulted in the overestimation of the risk of pulmonary embolism in long-distance air travellers. Hence, it was decided at the outset to seek information about a potential control's whereabouts on the date of death of the case so that analyses could be undertaken both including, and then excluding, any persons who were not in New Zealand on the date that their case died.

In the course of the study a total of 462 potential controls were selected from the electoral rolls (a further 79 were initially sent letters but had to be discarded because of a programming error which resulted in the selection of people born in adjacent years to the cases).

10.2.3 Decision to interview controls rather than their next of kin

The study was reliant on interviews to obtain information about long-distance air travel because such information is not routinely recorded in medical records and at the time the study was initiated it was not possible to obtain migration data relating to individuals. The decision to interview controls themselves, rather than their next of kin, was made after weighing up the advantages and disadvantages of both approaches. This process involved a trade-off of potential biases. The main argument in favour of interviewing the relatives of controls was that information about cases and controls should be sought in an identical manner to minimise the potential for information bias (Hennekens and Buring 1987). This condition is relatively easy to meet when it is possible to interview both cases and controls. In a study of fatal events, however, it is obviously necessary to interview proxy respondents. It would therefore follow that proxy respondents should also be used for controls. However it was felt that such an approach could, in fact, increase the possibility of bias. The reasons for this were two-fold. First, it was possible that the next of kin of controls would be less motivated to participate than the next of kin of cases, thus introducing a selection bias. Second, the next of kin of cases would clearly have reason to remember a flight undertaken by their relative in the four weeks before the onset of the fatal event. The next of kin of controls, on the other hand, would have no such memory prompt and, in addition, might be less likely than the next of kin of cases to have access to the passport and other records belonging to their relative. It is therefore conceivable that some controls might be misclassified as non-travellers and hence the risk of fatal pulmonary embolism in long-distance air travellers would be overestimated. It is also possible that the next of kin of controls would have less complete knowledge or recall about whether their relative had other risk factors for venous thromboembolism before the index date than the next of kin of cases (who again would have reason to have obtained and recalled such information). Potentially this would hinder the identification of those with major risk factors and consequently limit the evaluation of potential confounding.

For these reasons it seemed preferable to interview the controls themselves, as they would be expected to report their travel and medical histories more accurately than their relatives. It was also recognised, however, that such an approach might not entirely minimise the potential for recall bias in relation to some risk factors for venous thromboembolism. For instance, the reliability of information provided by proxy

respondents has been shown to be dependent on the relationship of the respondent to the case and the nature of the information being sought (Poulter et al. 1996b). In the present study, for example, it is possible that the husbands of older cases would have less knowledge about the use of hormone replacement therapy by their wives than the female controls would have about themselves. On the other hand, younger men might report the use of oral contraceptives by their partners just as accurately as the controls reported their own use. It is also possible that the next of kin of cases would report the presence of temporary risk factors for venous thromboembolism in the three months before the index date (for example, injury) more accurately than the controls who might have no reason to locate specific events in time.

After consideration of all these issues it was decided to interview the controls themselves, rather than their next of kin, since this approach gave the best possible chance of obtaining information of comparable quality for cases and controls about long-distance flights and other key exposures. As with next of kin, controls were interviewed by telephone.

10.2.4 Obtaining current contact details for controls

The methods that were used to search for the contact details of the 462 potential controls who were selected from the 1993, 1996, 1998 and 2000 electronic electoral rolls are shown in Figure 10.1. The names and addresses of 400 were found on the 2003 electoral roll and a further two were found in the electronic telephone directory. Two main methods were employed to search for the remaining 60 potential controls. The first involved a search, by residential address, of electronic electoral rolls from past years to obtain the names of any adults with whom the potential controls had lived before or after the index date. The 2003 roll was then searched to find the current contact details of these household members. Invitation letters were subsequently sent to 25 potential controls via the addresses of past household members, since the surnames and ages of these people suggested that they were relatives. Second, the office of Births, Deaths, and Marriages was approached to ascertain whether any of the untraced potential controls had died or changed their names. Because a fee was payable for record searches, the enquiries were initially confined to older people who had been consistently enrolled in the past before disappearing from the roll sometime after the index date. Seventeen such people were found to have died after the index date (Table

10.1), three of whom were determined to be ineligible because of their dates of birth. No attempt was made to contact the next of kin of the 14 potentially eligible deceased controls because it was thought that it would be unreasonable to ask them to participate in a study of a condition other than the one from which their relative had died. It was expected that such people would have been less likely to have travelled and hence any bias introduced by the exclusion of these potential controls would be conservative. The initial search of Births, Deaths, and Marriages records also identified the new surnames of three women. The married names of two other women were found when searching for household members, and one person was traced using an alumni database.

Thus, in summary, 17 of 462 of the potential controls who were selected died after the index date and before the 2003 electoral roll was compiled, 433 were sent letters at their own (*n=408*) or a relative's address (*n=25*), and for 12 a personal or relative's postal address could not be found.

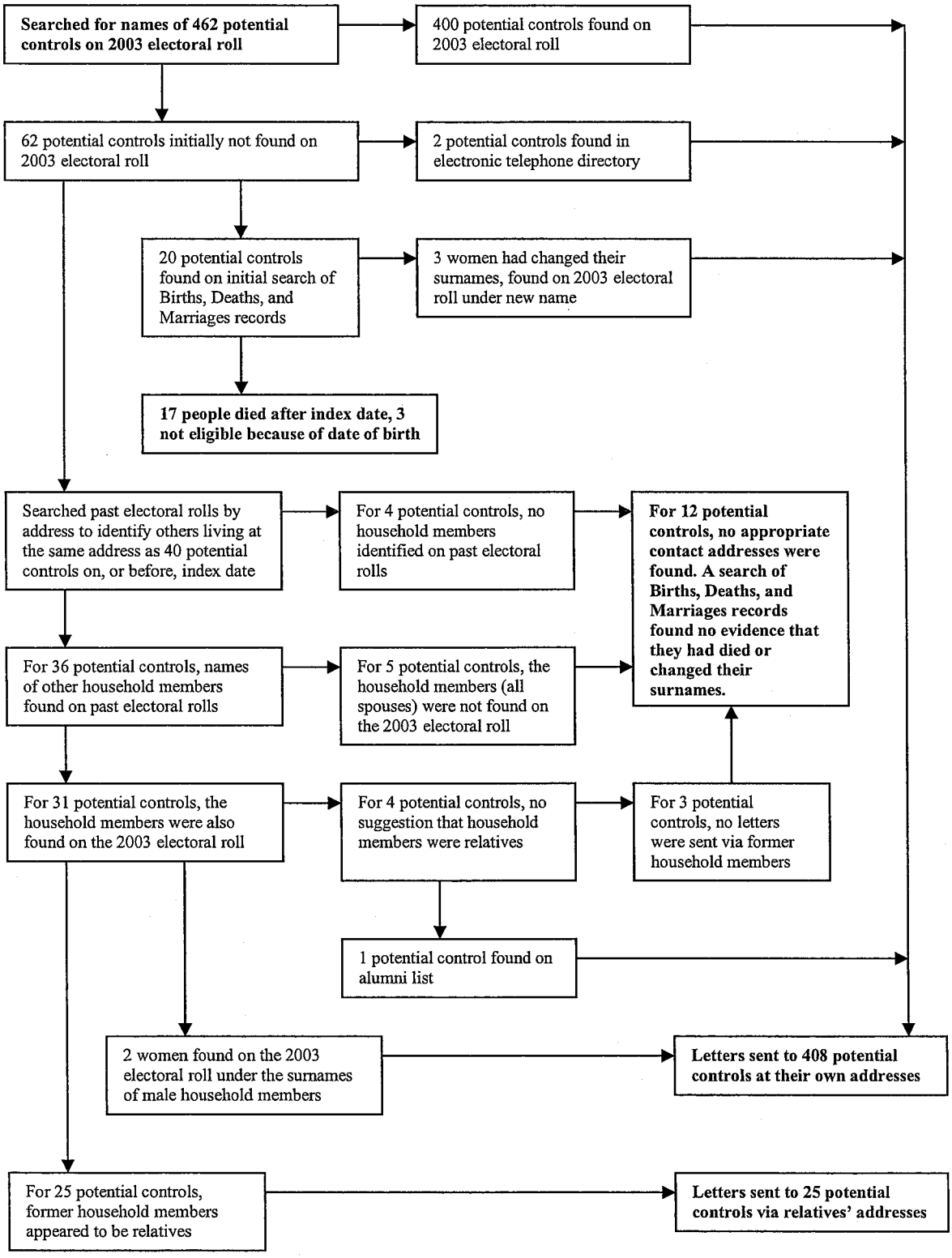

Figure 10.1 Methods used to trace potential controls

Table 10.1 Deaths of potential controls identified by a search of Births, Deaths, and Marriages records

Sex	Age at death (years)	Interval between index date and date of death	Causes of death (intervals between onset and death)*	Eligible date of birth
Male				
	52	1 month	Acute congestive heart failure Hypertensive heart disease (intervals not recorded)	Yes
	56	8 years, 8 months	Hypercalcaemia (1 month) Metastatic lung cancer (2 years) Heavy smoker (years) Ex-alcoholic (years) Hypertension (years)	Yes
	58	10 years, 8 months	Myocardial infarction (1 day) 2 earlier infarcts Mild emphysema (interval not recorded)	Yes
	61	2 years, 10 months	Gastrointestinal haemorrhage (days) Alcoholic liver failure (weeks) Chronic alcoholism (years)	Yes
	61	5 years, 5 months	Ischaemic bowel Mesenteric vessel occlusion Large neglected inguinoscrotal hernia (intervals not recorded)	Yes
	61	11 years, 0 months	Cardiac arrest (3 minutes) Myocardial infarction (3 minutes) Hypertension (14 years) Diabetes (14 years) Peripheral vascular disease (1 year)	Yes
	63	8 years, 11 months	Congestive heart failure (5 months) Coronary heart disease (5 years) Type 1 diabetes (> 10 years) Diabetic retinopathy, blind (3 years) Cerebrovascular accident (3 years)	Yes
	64	5 years, 9 months	Metastatic renal carcinoma (18 months) Renal carcinoma (2 years) Cerebral thrombosis (6 years)	Yes
	64	13 years	Subject to coroner's finding	No
	67	12 years, 6 months	Bronchopneumonia (1 week) Emphysema (10 years) Ischaemic heart disease (7 years)	Yes

Sex	Age at death (years)	Interval between index date and date of death	Causes of death (intervals between onset and death)*	Eligible date of birth
Female				
	57	7 years 11 months	Metastatic ovarian cancer (28 months)	Yes
	58	4 years, 7months	Metastatic lung cancer (months)	No
	59	1 year, 2 months	Pneumonia (interval not recorded)	Yes
	61	1 year, 3 months	Metastatic adenocarcinoma, probable large bowel primary (2 months)	Yes
	62	3 years, 10 months	Renal failure Metastatic breast cancer (intervals not recorded)	Yes
	62	3 years, 8 months	Chronic renal failure Type 2 diabetes Peripheral vascular disease (intervals not recorded)	Yes
	65	5 years, 5 months	Metastatic bowel cancer (18 months)	No

* Causes of death and intervals between onset and death as recorded on Death Registration forms obtained from Births, Deaths, and Marriages.

10.2.5 Contacting next of kin and controls

The methods used to contact next of kin were described in Chapter 8. Potential controls were sent a letter which invited them to take part in a study of "an important health condition that affects many New Zealanders" (Appendix A, letter 24). They were not told that the condition was venous thromboembolism, since this might have introduced a selection bias, with those who had a personal or family history of the condition being more inclined to participate. Similarly, neither the next of kin nor the controls were informed of the study hypothesis until their interview was completed. As with next of kin, potential controls were sent a letter about the study which asked them to return, in a reply-paid envelope, a form confirming their contact details and suitable times to be contacted by telephone. Those who replied were called at the appropriate time to discuss the study and oral consent was sought for a telephone interview at a later time (Appendix D, form 3). Occasionally, at the request of a potential participant, an interview was conducted during that first telephone contact. Potential controls who had not responded after two weeks were contacted by telephone (Appendix D, form 4) or, if they did not have a traceable telephone number, were sent up to two further letters (Appendix A, letter 25). To ensure that information about the study was given in a consistent manner, these initial telephone calls to next of kin and potential controls were all made by me. All attempts to contact participants by telephone were recorded on the oral consent form. As with next of kin, the initial and subsequent letters sent to controls, the reply-paid forms, and the oral consent forms were adapted from those used in two previous case-control studies (Paul et al. 1989; Cox et al. 2002).

10.2.6 Telephone interviews with next of kin and controls

Development of a draft questionnaire

A standardised questionnaire was developed for use during the telephone interviews with next of kin and controls. The questionnaire was designed to obtain details of any long-distance air travel in the four weeks before the index date, as well as demographic data, information about hereditary and acquired risk factors for venous thromboembolism, the presence of other medical conditions, and the use of medicines.

The development of the questionnaire involved several stages. First, interviewer-administered questionnaires used by colleagues in previous case-control studies were examined (Paul et al. 1989; Dockerty et al. 1998; Cox et al. 2002). Two of the studies

had involved telephone interviews of the cases and controls (Paul et al. 1989; Cox et al. 2002), while the third had been used in face-to-face interviews of the parents of the cases and controls (Dockerty et al. 1998). A few introductory statements from these questionnaires were modified for use in the present study.

Second, the Individual Form used in the 2001 New Zealand Census of Population and Dwellings was examined (Statistics New Zealand 2001b), with particular attention directed towards the wording of questions about ethnicity, educational attainment, and employment. For the purposes of this study it was important to obtain information about both "ethnic group" (self-identified cultural affiliation) and "ethnic origin" (biological ancestry). Self-identified ethnicity is associated with socio-economic status (Reid et al. 2000), and hence the opportunity to undertake international air travel, while some thrombophilic mutations are found more frequently among New Zealanders of European descent than among Maori and those of Pacific Island ancestry (Van de Water et al. 1997). The Census question about ethnic group was included verbatim in the study questionnaire. This asked participants to indicate which ethnic group or groups the case, or they (if controls), belonged to. Since people with both non-European and European ancestors sometimes self-identify as belonging solely to one of the non-European ethnic groups (for example, Maori), a second Census-derived question was included for cases and controls who were reported to belong exclusively to one of the non-European ethnic groups. This enquired whether they had any European ancestors.

The remainder of the draft questionnaire was composed by me with reference to principles of good questionnaire design (Bennett and Ritchie 1975; Foddy 1993). The questionnaire opened with a paragraph that introduced the interviewer and her affiliation with the Otago Medical School, and thanked the next of kin or control for agreeing to participate in the study. An assurance of confidentiality was also given. The purpose of the study was explained in general terms, namely that it was a study of health problems before a particular date. The questionnaire was then divided into sections of related questions, starting with some general questions about health and concluding with enquiries about more sensitive subjects such as educational attainment, employment, marital status, and ethnicity. Each new section began with a statement that introduced the broad subject area of the subsequent questions. The questions themselves were written at a level that was aimed at people with a basic education.

Hence, sentences were kept as short, grammatically simple, and unambiguous as possible. Although medical terms were included in the questionnaire, explanations were also given in lay language. Negative and leading questions were avoided. Since open-ended questions about the health of the case or control before the index date would have required active recall, respondents were initially asked closed questions about medical conditions and exposures. If the answer to certain questions was "Yes", they were then asked some supplementary open-ended questions. Additional space was also allowed at the end of the questionnaire for extra comments. Statements were included throughout the questionnaire which reminded respondents of the time periods of interest. These statements were made as specific as possible. For example, when enquiries were made as to whether the case or control had ever been treated for a particular medical condition before the index date, it was stressed that the time period of interest was from the time they were born right through until the specified date. Similarly questions about exposures in the three months or four weeks before the index date stressed the exact dates involved. As will be discussed later, respondents were also asked to mark these dates on a customised calendar.

Finally, the draft questionnaire was discussed with two Maori and two Samoan hospital and community-based health workers, as well as two Maori health researchers. This was to help ensure that the content and wording of questions was not culturally inappropriate for Maori or Samoan people, as it was already known that some of the cases and their next of kin belonged to these ethnic groups. Moreover it was clear that some Maori would be selected as controls since some of the Maori cases had been enrolled on the Maori Electoral Roll and thus their controls would be selected from a Maori electorate.

Piloting the draft questionnaire

The draft questionnaire was piloted over the telephone with volunteers from a variety of community groups including the Medical Auxillary (a group of older people in Dunedin who voluntarily participate in medical research), Toastmasters, and an outdoor recreational club, as well as people contacted by Maori health workers. The volunteers were each allocated an index date and were sent a life-events calendar for the 13 months leading up to this date. Local and national public holidays and school terms were marked on this life-events calendar. To assist recall about events before the index date,

volunteers were asked at the beginning of the interview to circle the index date on the calendar, as well as dates three months, and four weeks, before the index date. They were also asked to recall any significant events that occurred around that time. The calendar was referred to throughout the interview.

In total 18 women and 13 men of varying ages (range 22 – 83 years, median 69 years), educational levels, socio-economic status, and ethnicity were interviewed during this pilot phase. A deliberate effort was made to interview older people because they were likely to have experienced more health problems and this provided a greater opportunity to test the questions about past medical conditions.

Ten of the volunteers were interviewed about their spouse (designated as a "case") and their spouse was interviewed about himself or herself. Couples were asked not to sit in the same room during the interview and the first spouse to be interviewed was asked to refrain from telling their partner about the interview. Five men were interviewed about their wife (and the wife about herself), and five women were interviewed about their husband (and the husband about himself). Although the "case" hadn't died, and as such there was no particular reason to remember a four-week period up to 13 years earlier, seven of ten couples were in agreement that the "case" had not undertaken international air travel in the four weeks before the index date. Two women reported that they hadn't undertaken an international flight during the relevant period, although the husband of one thought that she had undertaken a three to four hour flight, while the other man thought it "possible" that his wife had undertaken an international flight. One woman thought her husband might have flown internationally, while he reported that he didn't. Although they were not asked to do so, the volunteers spontaneously reported that they would have been willing to check their passports to ensure that they gave accurate information. Thus, it was decided to ask participants in the descriptive and case-control studies to check passports and other records if necessary before answering any questions about international air travel. In addition, people were to be offered the choice of checking their records while the interviewer waited on the telephone, or of making a time to be contacted later.

In relation to questions about medical history, medications, the use of oral contraceptives and hormone replacement therapy, and demographic data, there was

good agreement between the information provided by both members of a couple. While some partners thought that the "case" was heavier or lighter, or taller or shorter than the "case" reported himself or herself to be on the index date, this had no impact on which BMI category seven of the ten "cases" were classified as belonging to (< 20, 20 – 24.9, 25 – 29.9, ≥ 30 kg/m²). One man had no idea what his wife had weighed, and in the remaining two couples the difference in estimated BMI was not great (18.8 c.f. 20.9 and 23.3 c.f. 26.1 30 kg/m²), although it did mean that there was disagreement about the category to which the "case" belonged. Consequently a question was added to the final questionnaire which enquired whether, in relation to height, the case or control was "of normal weight", "overweight", or "underweight".

Ongoing feedback about the draft questionnaire was sought from the registered nurse who conducted some of the pilot interviews and from all of the volunteers. In particular, the nurse interviewer was asked the following questions (Foddy 1993):

> Did any of the questions seem to make respondents uncomfortable?
> Did you have to repeat any questions?
> Did the respondents misinterpret any questions?
> Which questions were the most difficult or awkward to read?
> Have you come to dislike any specific questions? Why?
> Did any sections seem to drag?
> Were there any sections in which you felt that the respondents would have liked the opportunity to say more?

In response to the feedback, further modifications were made to the draft questionnaire, which was then tested with subsequent volunteers. Most of the modifications involved the insertion of additional introductory statements at the beginning of sections or before certain questions. These statements were of two main types: statements which acknowledged potentially difficult tasks and those which explained why certain questions were being asked. Other minor amendments included altering the sequence of some questions and modifying the enquiries about superficial and deep vein thrombosis. The latter change was made because several of the volunteers reported that their partner had been treated for a blood clot in the legs, but they were unable to say whether it had occurred in a superficial or deep vein. Hence, the two questions were combined into

one so that respondents were first asked whether their relative (or they themselves, if they were a control) had been treated for a blood clot in a leg vein before the index date, before being asked further questions such as about its location.

With the exception of one volunteer, who said that she generally declined to answer questions about qualifications and employment because they highlighted gender inequalities, the volunteers had no objections to the content of any of the questions. Of particular note, they all indicated that had they been genuine participants in the study they would have given their permission for the dates of their hospital admissions (if any) to be checked.

The final version of the questionnaire

A copy of the final version of the interviewer-administered questionnaire can be found in Appendix E. Briefly, the questionnaire included enquiries about the following before the index date: international air travel, domestic air travel in countries other than New Zealand, medical conditions associated with an increased risk of venous thromboembolism (including a history of venous thrombosis or pulmonary embolism, varicose veins, known thrombophilia, systemic lupus erythematosus, inflammatory bowel disease, and malignancy), acquired risk factors for venous thromboembolism in the three months before the index date (including major surgery, major injury, pregnancy, hospital admissions for other reasons, and being confined to bed or a wheelchair for more than one week), other medical conditions (including ischaemic and other heart disease, stroke, hypertension, diabetes, renal disease, and liver disease), medication use in the three months before the index date (including oral contraceptives and hormone replacement therapy), parity, past exposure to female hormones, smoking habits, estimated weight and height on the index date, post-secondary school educational attainment, occupation, ethnicity, and a family history of venous thromboembolism. For subjects who lived with a spouse, partner, or parents, information was also sought about their occupation on the index date.

For those who had undertaken long-distance air travel, participants were asked to name the airports at which the journey began and ended (the final destination), and the dates of departure and arrival. In addition, they were asked to name any airports at which the traveller had landed during the journey and to specify the length of time spent at each of

these airports. If participants were unable to give an exact answer to the latter question, they were asked to choose between several time categories ("< 2 hours", "2 to < 5 hours", "5 to < 9 hours", "9 to < 12 hours", "12 hours or more", or "Don't know"). For each leg of the journey, participants were asked about the duration of the flight, the class of travel, whether the traveller had sat in an aisle seat, and whether they had taken a hypnotic drug immediately before, or during, the journey. Participants who were unsure about the duration of a flight, were asked to select a time category ("< 4 hours", "4 to < 9 hours", "9 to < 12 hours", "12 hours or more", or "Don't know"). Details of any domestic flights undertaken immediately before or after international flights were also obtained. Otherwise no information about domestic flights within New Zealand was sought, because of the short travelling times involved and the possibility of recall bias.

As discussed in Chapter 8, the next of kin were also asked whether the cases had undertaken journeys of more than four hours' duration by other means of transport in the four weeks before the index date. This information was not sought from controls because it was considered unlikely that they would remember such episodes. Hence, the data regarding cases were included in the descriptive study only.

Permission was sought from controls to check the dates of any hospital admissions before the index date. This information was already available for cases.

Computer-assisted telephone interviews

Computer-assisted telephone interviews, as the name suggests, are telephone interviews in which the interviewer asks the relevant questions as they are displayed on the computer screen and then records the participants' responses directly into the computer. In the present study it was decided to undertake such interviews for several reasons. First, the wording of the interview questions varied slightly according to whether the respondent was a next of kin or a control, whether the case or control was male or female, and the relationship of the case to the next of kin. In addition, each case and their controls had a unique set of relevant dates. Thus, it was necessary to customise the questionnaire for each interview. Moreover, the paper-based version of the questionnaire proved rather cumbersome to administer because of the number of potential skips. For example, some questions were not asked if the subject was male or

if the answer to a preceding question was "No". In these situations it was sometimes necessary to flick through several pages to find the next relevant question. Such pauses interrupted the flow of the interview and were particularly awkward because the respondent was unable to see what the interviewer was doing.

Various options for undertaking computer-assisted telephone interviews were therefore explored and it was decided to accept an opportunity to pilot some newly-developed software (Abbey CATI software®), which was developed by Mr Charlie Blakey from the Life in New Zealand (LINZ) Activity and Health Research Unit at the University of Otago (Blakey 2003). All of the problems outlined above were easily addressed using this software. While setting up the computer-based questionnaire, I was able to create links between the questions and a list of variables. which included the subject's status (case or control), sex, and date of birth, as well as the date of death of the case, the index date, the dates three months and four weeks before the index date, and a variable to indicate whether the date of death was the same as the index date. A variable was also included to record the relationship of the case to the next of kin. Then, as participants were enrolled in the study, the values of the variables for each subject were entered into the system. Consequently the appropriate pronouns, relationships, and dates were automatically displayed on the interviewer's computer screen during each interview. Moreover it was possible to insert certain commands before or after particular questions to ensure that only the relevant questions were displayed. For example, "pre-logic" statements that were placed before the questions about pregnancy, oral contraceptives, and hormone replacement therapy ensured that these questions were only shown if the case or control was female. Likewise, "response logic" statements that were placed at the end of some questions ensured that if a respondent answered "Yes" to a particular question, then supplementary questions about that subject would be displayed. Conversely, if the respondent answered "No", the supplementary questions would remain hidden and the next major question would be shown. Additionally, for some questions, a "Don't know" response would prompt another set of questions.

A further advantage of undertaking computer-assisted interviews using the Abbey system was that responses to questions were entered directly into the computer during an interview. This removed the potential for transcription errors, and the amount of data

checking that would have been necessary, had the responses been recorded on a paper-based questionnaire and later entered into a computer database. Moreover the Abbey software allowed me to specify, for each question, which type of response was required. Possibilities included numeric responses, single or multiple choices from lists of specified responses, and single or multiple line narrative comments. For all but the narrative comments, this facilitated the simultaneous entry and coding of responses and minimised the amount of coding that was required following the interview. For example, if the possible answers to a particular question were "Yes", "No", or "Don't know", these options were all listed on the screen with corresponding check boxes. If the respondent's answer was "Yes", the interviewer simply needed to click on the "Yes" check box to both record and code the response in the underlying data file. For questions to which there were a large number of possible responses (for example those about medicine use, qualifications, occupation, and detailed enquiries about conditions such as cancer) various options for coding these data during the interview were considered. However it was felt that these would be difficult to carry out in the context of an interview and hence would be vulnerable to coding errors. Thus, it was decided that narrative responses to these questions would be recorded during the interview and that I would code these responses when all the interviews were completed.

The use of logic statements also facilitated checks for internal consistency, thus removing the need to rely solely on the interviewer's memory to identify contradictory responses. For example, in the first section of the questionnaire respondents were asked whether the case or control had ever been treated for specific medical conditions; later they were asked about the indication for any medication taken in the three months before the index date. If a respondent initially stated that they (or their relative) had never been treated for high blood pressure, but later reported that they were taking medication to treat this condition in the three months before the index date, a question about this inconsistency was displayed on the interviewer's computer screen. Similarly questions were asked about the birth of any children, the use of oral contraceptives, and hormone replacement therapy at any time before the index date; while in a later section enquiries were made about exposure to these risk factors in the three months before the index date.

Measures to detect data entry errors were also established. As already discussed, if a respondent replied "Yes" to certain questions, then other related questions would be displayed. Hence, if a respondent's affirmative response was incorrectly entered as "No", the interviewer was alerted to the error when the supplementary questions failed to appear on the computer screen. Questions to which supplementary enquiries were not attached were grouped together at the beginning of the questionnaire, following which respondents were asked to confirm that the answers the interviewer had recorded were correct. To help prevent the entry of improbable values for questions that required numeric responses, the permissible number of digits was specified.

Finally, once the computer-based questionnaire had been set up, the system was tested by conducting telephone interviews with colleagues who deliberately gave contradictory answers and provided improbable values.

Training and supervising the nurse interviewer

The nurse interviewer undertook supervised practice interviews with colleagues and then with volunteers. The importance of adhering to the exact wording of the questionnaire was emphasised, as well as the need to adopt a standard tone and manner when asking the questions. Oral and written guidance was given about how to interpret and record responses. Difficulties that might be encountered during the interviews were also discussed and instructions for dealing with these were recorded in writing. The training initially involved a paper-based version of the questionnaire, but once the computer-based version was set up, the necessary skills for undertaking computer-assisted interviews were taught and practised. The importance of keeping paper copies of the questionnaire on hand in case of computer problems or power failures was also stressed.

The nurse interviewer observed the interviews I undertook with study participants at the beginning of the study and, in turn, I observed the first 25 interviews undertaken by the nurse and independently recorded the responses of the participants. There were no discrepancies between these data and those recorded by the nurse interviewer. Subsequent interviews were periodically observed to confirm that they continued to be conducted in a standardised manner. The nurse interviewer was also urged to seek guidance if she encountered any unanticipated problems.

Interviews

The interviews were all undertaken by the nurse interviewer or me using the standardised questionnaire. To assist recall about events before the index date, the life-events calendar was used as described for the pilot study. If participants had mislaid their calendar, the interview was postponed and a replacement calendar was emailed, faxed, or posted. People who did not wish to have their interview rescheduled were asked to write the relevant dates on a piece of paper and this was referred to during the interview.

The case-control study was based solely on data obtained from the telephone interviews and the confirmation of hospital admission dates. No information about cases derived from other sources was used for comparisons between cases and controls.

Post-interview data management

Once the interviews were completed, the data were imported into the SPSS statistical package (version 13.0). Data coded during the interview were checked for improbable values, and post-interview coding was all undertaken and double-checked by me.

The duration of each long-distance flight undertaken by subjects in the four weeks before the index date was confirmed by reference to flight schedules on the web sites of the Star and Oneworld alliances. These schedules were also used to assign more exact flight times for subjects for whom categories of flight duration were reported. In situations where there was some variation in the flight durations recorded in the schedules, the convention was to assign the shortest travel time.

As anticipated, while some participants who responded affirmatively to the question about treated venous thrombosis were able to indicate whether the clot was superficial or deep, others could not. Information was sought about the type of treatment given, but this did not always help to determine the type of thrombosis. Because of this, and because it is possible that superficial and deep vein thrombosis are part of the same process, it was decided to classify all those who had a history of treatment for superficial, deep, or unspecified venous thrombosis (or pulmonary embolism) as having a history of venous thromboembolism.

Narrative comments regarding malignancy, non-ischaemic cardiac disease, and renal and hepatic conditions were coded to ICD-9 rubrics, while the drug dictionary obtained from the Centre for Adverse Reactions Monitoring (discussed in Chapter 4) was used to assign numerical codes to medicines taken in the three months before the index date.

The highest qualification that a subject obtained after leaving school was assigned a numerical code corresponding to one of the following categories: Trade certificate or diploma, nursing certificate or diploma, New Zealand certificate or diploma, technical certificate or diploma, teaching certificate or diploma, university certificate or diploma, Bachelor's degree, post-graduate certificate or diploma, post-graduate degree, other certificates or diplomas from polytechnics and other institutions, and other qualifications.

The occupations of cases and controls on the index date (or their last job before this date) were assigned a numerical score according to the New Zealand Socio-Economic Index 1996 (NZSEI-96) (Galbraith et al. 2003). The occupations of spouses, and of co-habiting partners or parents of subjects, were also coded. The NZSEI-96 is an occupationally-based measure of socio-economic status based on the New Zealand Standard Classification of Occupations (Statistics New Zealand 2001c) and census data. Occupations are assigned scores ranging from 10 (lowest end of the socio-economic scale) to 90 (highest end). These scores may be used as continuous variables or, with recommended cut-off points, be used to assign subjects to one of six socio-economic categories. The latter approach was used in the present study.

10.2.7 Statistical analysis

The data were transferred from SPSS into version 8 of the SAS statistical software by a biostatistician in the Department of Preventive and Social Medicine, Dr Melanie Bell, who then undertook the statistical analyses in collaboration with me.

Cases and controls were classified as belonging to one of six socio-economic categories on the basis of their NZSEI-96 score. For subjects living with a partner or parents, socio-economic status was classified using the highest score in the household. The ethnicity of cases and controls who were reported to belong to more than one ethnic group was classified according to a prioritised concept of ethnicity (Allan 2001). Thus,

subjects who were identified as belonging to both Maori and other ethnic groups were classified as Maori. Cases and controls who belonged to both a Pacific Island ethnic group, and other non- Maori groups, were classified as Pacific.

Estimates of weight and height on the index date that had been reported in imperial measures were converted to metric measures. BMI was then calculated and classified as underweight (< 20.0 kg/m^2), normal weight (20.0 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2), and obese (≥ 30.0 kg/m^2). The normal weight category was taken as the reference category for BMI. Three controls and the next of kin of 24 cases provided estimates of height, but not weight, on the index date and the next of kin of two cases provided neither weight nor height. A further three controls were unable to supply an estimate of height on the index date, but did provide an estimate of weight. For these six controls and 26 cases, the BMI category was assigned using answers to the question about weight in relation to height. There were three possible responses to this question: "about right", "overweight", or "underweight". However because some respondents made additional comments which indicated that the subject was actually obese, some "overweight" subjects were reclassified as "obese". Only one participant (the relative of a case) declined to answer questions about weight, although she did provide information about height.

In addition, as an alternative to treating BMI as a categorical variable, the missing BMI values were estimated using the median BMI measure for each BMI category (cases and controls combined) as shown in Table 10.2. In brief, the data of persons for whom both estimates of weight and height, and narrative comments about weight in relation to height, had been provided were used to calculate the median BMI for each BMI category. The median BMI for a particular BMI category was then assigned to those persons in that category for whom weight and height estimates were missing.

Table 10.2 Median BMI measure for each BMI category

BMI category	Median BMI for category (kg/m²)
Underweight*	19.0
Normal weight†	22.8
Overweight‡	27.1
Obese§	33.2

* BMI < 20.0 kg/m²
† BMI 20.0 – 24.9 kg/m²
‡ BMI 25.0 – 29.9 kg/m²
§ BMI ≥ 30.0 kg/m²

Odds ratios and 95% confidence intervals were calculated using conditional logistic regression (using the statistical software SAS, version 8). Exposures of any long-distance flight and flights greater than eight hours' duration were modelled separately. The key analyses were restricted to subjects who did not have disseminated or recently diagnosed (less than five years before the index date) cancer (excluding localised malignant melanoma), were not pregnant, and had not undergone major surgery in the three months before the index date (since the ascertainment of cases excluded patients with these conditions). As matched analyses were performed, the controls of excluded cases were also excluded. Subjects who had not undertaken an international flight in the four weeks before the index date were taken as the reference category. Those who undertook flights of eight hours or less were excluded from the analyses that examined flights of more than eight hours.

Unadjusted and adjusted odds ratios were estimated. Confounders were identified using both backwards deletion and forward selection strategies (Rothman and Greenland 1998) and were confirmed in univariate analyses. The following potential confounders were examined: a history of venous thromboembolism; a history of varicose veins; BMI (both as a categorical variable and then as a continuous variable); socio-economic status; the use of oral contraceptives, hormone replacement therapy, aspirin, and antipsychotic drugs in the three months before the index date; and major injury including a fracture, prolonged immobility, and a hospital admission owing to a medical condition in the three months before the index date. Only those variables which resulted in a greater than 5% change in the odds ratios were included in the final models.

In secondary analyses, additional exclusion criteria were applied so that subjects with a history of venous thromboembolism were excluded, as well as those with a history in the three months before the index date of major fracture, other major injury, a hospital admission owing to a medical condition (an admission for reasons other than surgery, fracture, other injury, or pregnancy), or of prolonged immobility (confined to bed or a chair for more than a week). Controls who were not in New Zealand on the date of death of their case were also excluded from one analysis.

10.2.8 Sample size calculations

Sample size calculations were undertaken using PS software (Dupont and Plummer 1998) for a matched case-control design with a case:control ratio of 1:4, alpha of 0.05, a correlation coefficient for failure of 0.01, and power of 80%. Because the proportion of New Zealand residents who undertook international air travel increased during the study period, sample size calculations were undertaken using three different estimates of exposure (that is, the proportion of the resident population aged 15 – 59 years who undertook long-distance air travel during a four-week period). Exposure estimates were obtained for the years 1990, 1995, and 2000 by dividing the total number of short-term arrivals by New Zealand residents aged 15 – 59 years in the appropriate year by the estimated resident population aged 15 – 59 years for that year (all data provided by Statistics New Zealand), and then dividing the quotient by 13. The prevalence of exposure in the years 1990, 1995, and 2000 was thus estimated to be 2.0%, 2.4%, and 3.2% respectively. Table 10.3 shows the number of cases required to detect given odds ratios for each of these levels of exposure. At the time the study was planned, it was known that pulmonary embolism was the underlying cause of death in 103 New Zealand residents aged 15 – 59 years who died between 1990 and 2000. Hence, assuming a prevalence of exposure of 2.4%, a case:control ratio of 1:4, alpha of 0.05, and a correlation coefficient for failure of 0.01, it was calculated that the study would have sufficient power to detect an odds ratio of 3.9.

Table 10.3 Number of cases required according to odds ratios and the proportion of exposed controls

Odds ratio	Number of cases required*		
	2.0% of controls exposed†	2.4% of controls exposed‡	3.2% of controls exposed§
3.5	149	126	97
3.6	140	118	92
3.9	132	112	86
3.8	125	106	82
3.9	118	100	77
4.0	112	95	74
4.1	106	90	70
4.2	101	86	67
4.3	97	82	64
4.4	92	78	61
4.5	88	75	58

* With a case:control ratio of 1:4, $\alpha = 0.05$, correlation coefficient for failure = 0.01, and power = 80%.
† Exposure estimate based on 1990 data obtained from Statistics New Zealand (short-term arrivals data and population estimates for New Zealand residents aged 15 – 59 years).
‡ Exposure estimate based on 1995 data obtained from Statistics New Zealand (short-term arrivals data and population estimates for New Zealand residents aged 15 – 59 years).
§ Exposure estimate based on 2000 data obtained from Statistics New Zealand (short-term arrivals data and population estimates for New Zealand residents aged 15 – 59 years).

10.2.9 Ethical matters

The principles of respect for autonomy and the minimisation of harm were observed in the design and conduct of the both the descriptive and case-control studies. The letters of invitation to both next of kin and controls outlined why (in general terms) the study was being undertaken, the potential benefits of the research, and what was involved for participants; emphasised that participation was voluntary, that participants could chose not to answer particular questions or could withdraw from the study at any time if they wished; gave an assurance of confidentiality; provided the contact details of the local Health and Disability Services Consumer Advocate; and contained an invitation to make a reverse charges telephone call to me should they wish. Potential participants were not informed of the study hypothesis, since this might have affected their decision to participate and therefore have introduced bias. For similar reasons, controls were not told that pulmonary embolism was the condition under investigation. This information was, however, provided at the end of the interview to all those who were interested.

Various measures were taken to minimise potential harm to participants. The research was confined to cases who had died at least three years earlier, and therefore no next of kin who were very recently bereaved were approached. Nevertheless, receiving the letter of invitation and answering questions about their partner or relative had the potential to cause psychological distress for the next of kin. Hence, it was decided not to enquire about the particular circumstances of death, and an experienced nurse interviewer, who was accustomed to dealing with sensitive issues, was employed to conduct the interviews along with me. Next of kin were also able to have other family members or friends with them during the interview, and it was again stressed that (as with controls) they could choose not to answer particular questions and could withdraw from the research at any stage if they wished.

Following positive responses to letters previously sent to a few next of kin in order to identify the general practitioners of the cases, it was surmised that the next of kin might derive some benefit from knowing that the death of their relative was regarded as sufficiently important to be investigated further – and that the information obtained from the study might help to prevent future deaths.

Written consent was not sought from participants because it was thought preferable that people had the opportunity to seek more information before making a commitment to take part in the research. Hence, all potential participants with traceable telephone numbers were telephoned by me to discuss the research and to answer any questions. Those wishing to take part gave oral consent, which was recorded in writing. At the end of the interview, oral consent was also sought from controls to collect information on the dates of any hospital admissions before the index date and this was also recorded in writing. No-one refused. All participants were asked whether they wished to receive a summary of the results of the study when it was completed.

Passwords were used to restrict access to the raw interview data. The passwords were known only to the nurse-interviewer, me, and the researcher from the Life in New Zealand (LINZ) Activity and Health Research Unit who had designed the computer-assisted telephone interview software and who provided ongoing technical support and back-up of the data. Files in which the names and contact details of potential participants were recorded, and the forms completed by such people, were stored in a locked filing cabinet. Neither the nurse-interviewer nor the researcher from LINZ had access to any information about cases that had been obtained from medical and death records.

As with the descriptive study, ethical approval was granted by each of the regional ethics committees.

CHAPTER 11 CASE-CONTROL STUDY OF LONG-DISTANCE AIR TRAVEL STUDY: RESULTS AND DISCUSSION

11.1 RESULTS

11.1.1 Participation of next of kin and controls

Responses of next of kin and controls to letters of invitation

The responses of the next of kin of 99 cases who were initially considered eligible for inclusion in the case-control study are shown in Figure 11.1. For 87 of the 99 cases, letters of invitation were sent to just one relative. For the remaining cases, letters were sent in turn to two (seven cases), three (four cases), and six different relatives (one case).

The responses of the 433 potential controls who were sent letters of invitation are shown in Figures 11.2 – 11.5. Of the 408 potential controls to whom letters were sent directly, only 161 (39.5%) replied to the first letter (Figure 11.2), a second letter was sent to 64 who did not have traceable telephone numbers (Figure 11.3), and 37 were sent a third letter (Figure 11.4). Six (24%) of the 25 potential controls to whom letters were sent via former household members replied to the first letter, five were sent a second letter, and three were sent a third letter (Figure 11.5). It transpired that eight of these 25 potential controls had changed their surnames and all were subsequently located on the 2003 electoral roll under their new names. It was also ascertained that five of the 62 people who were not found on the 2003 electoral roll were not enrolled because they were living overseas.

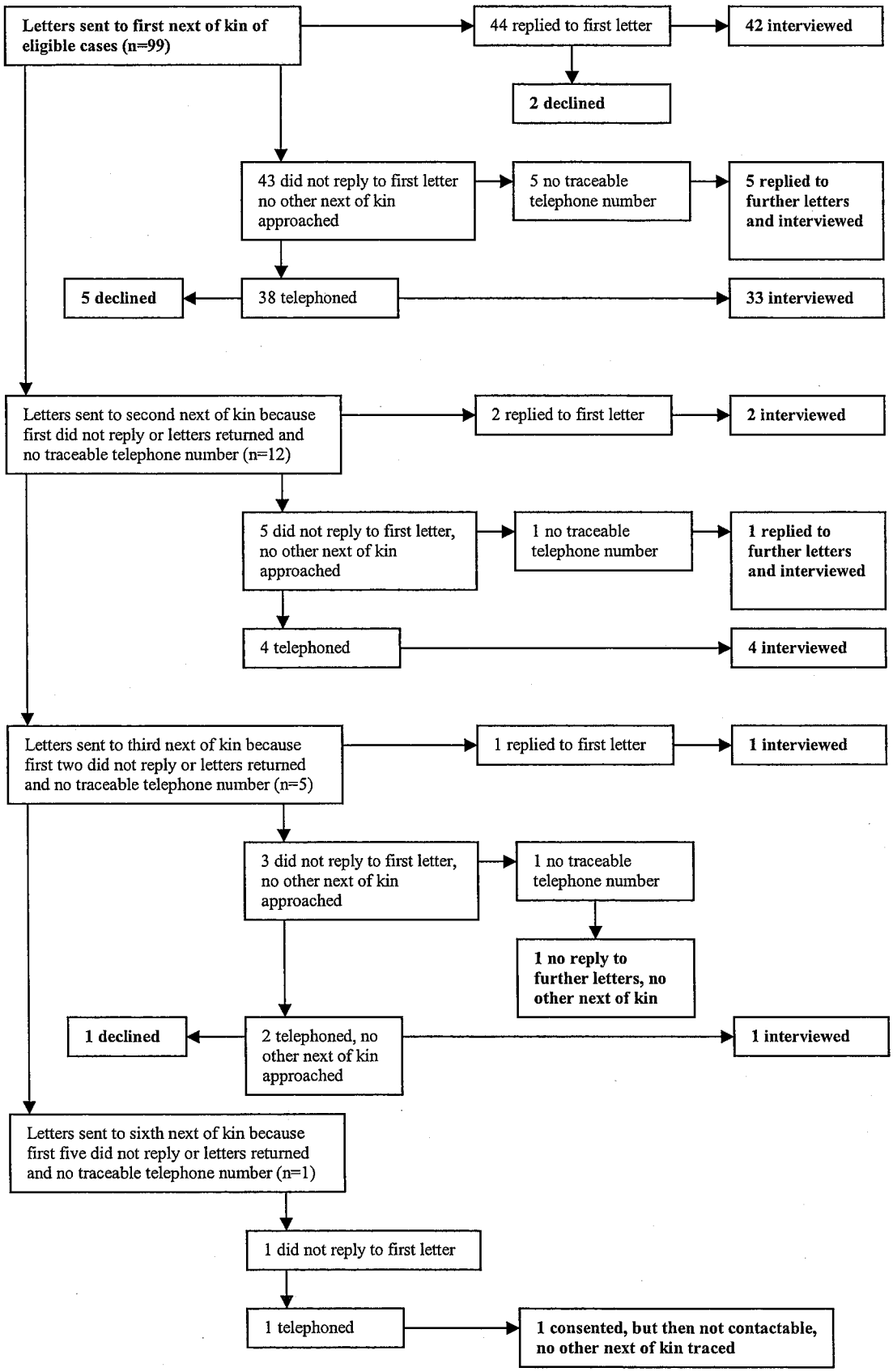

Figure 11.1 Responses of next of kin

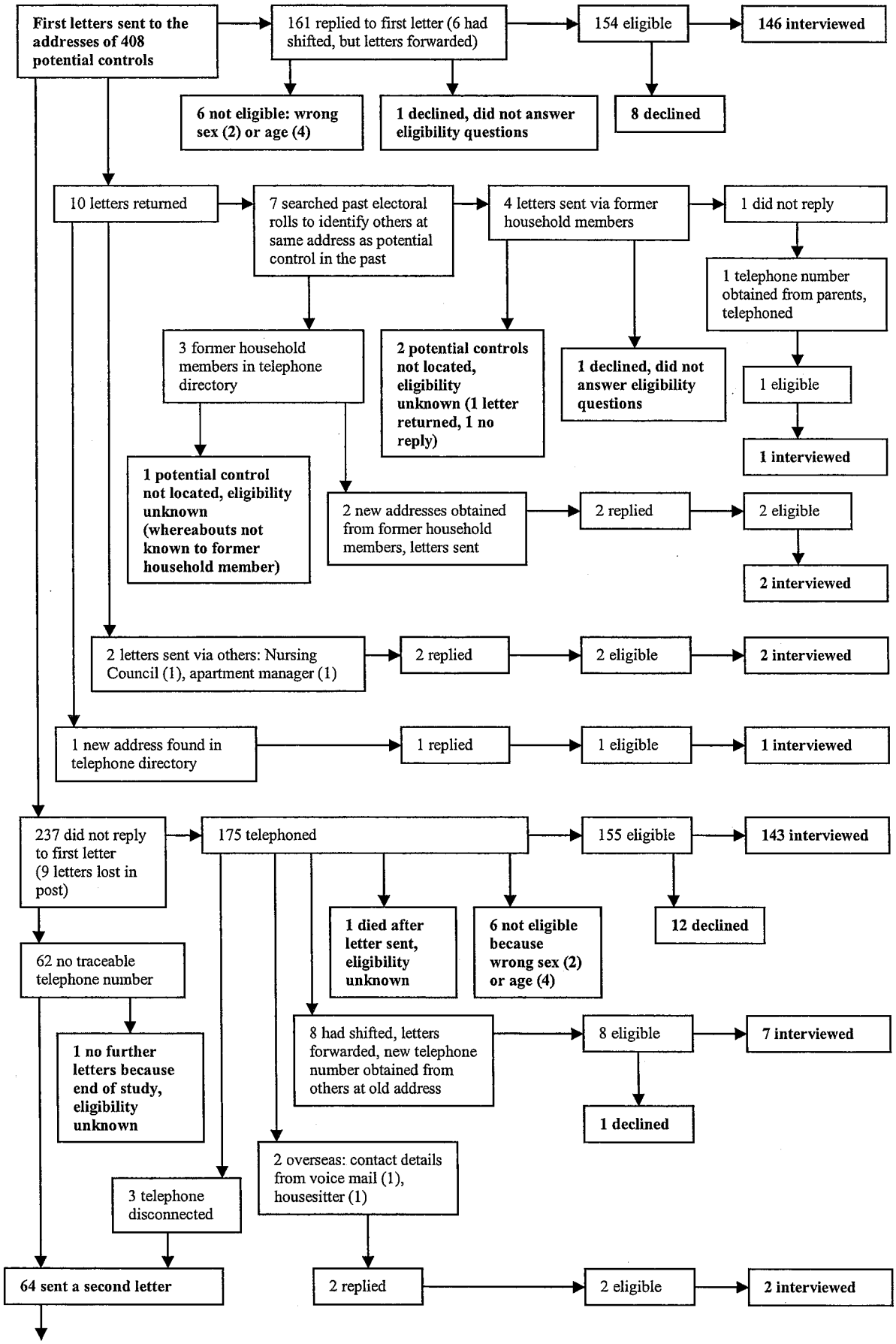

Figure 11.2 Responses of 408 potential controls to whom first letter was sent directly

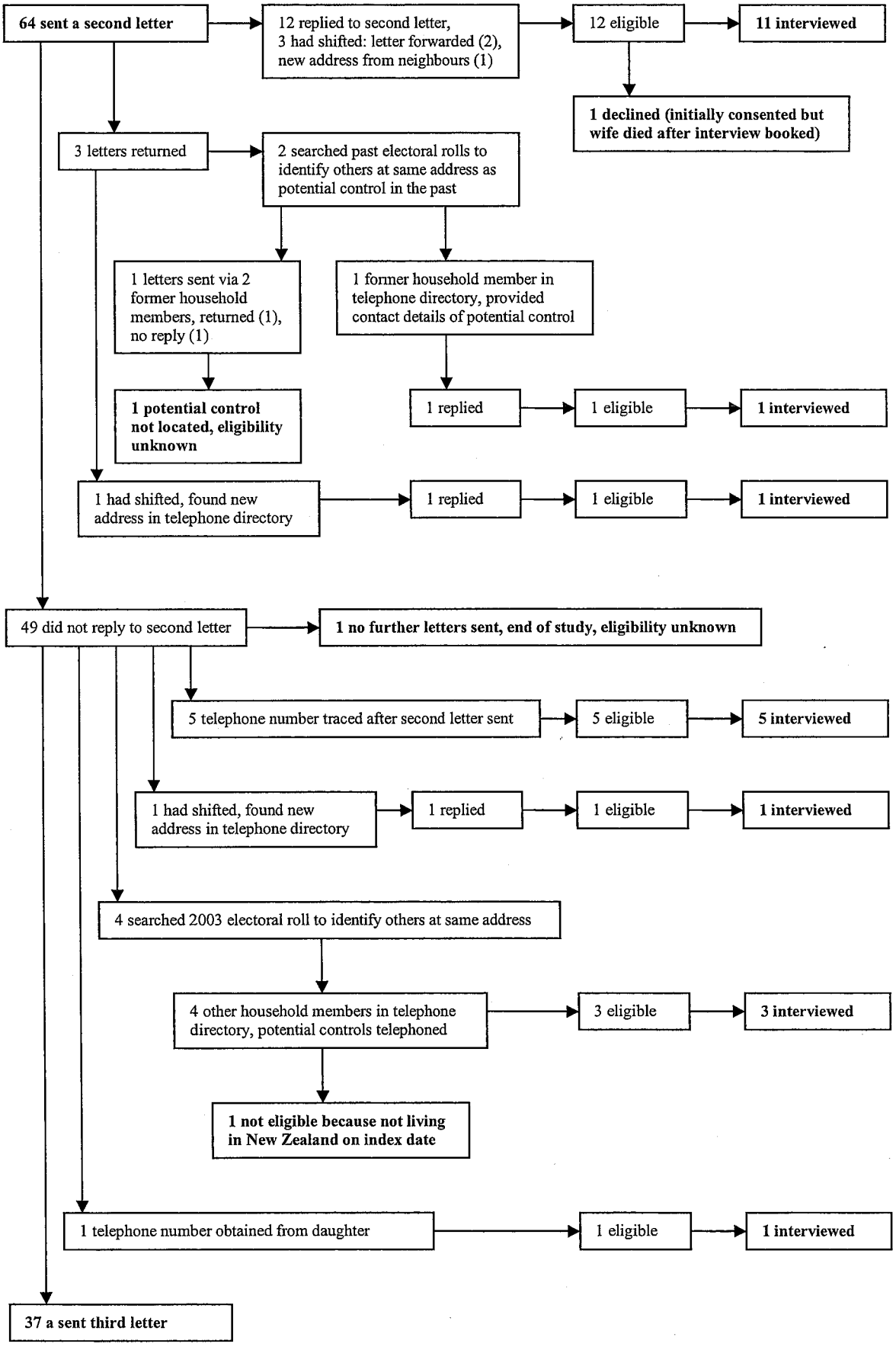

Figure 11.3 Responses of 64 potential controls to whom a second letter was sent

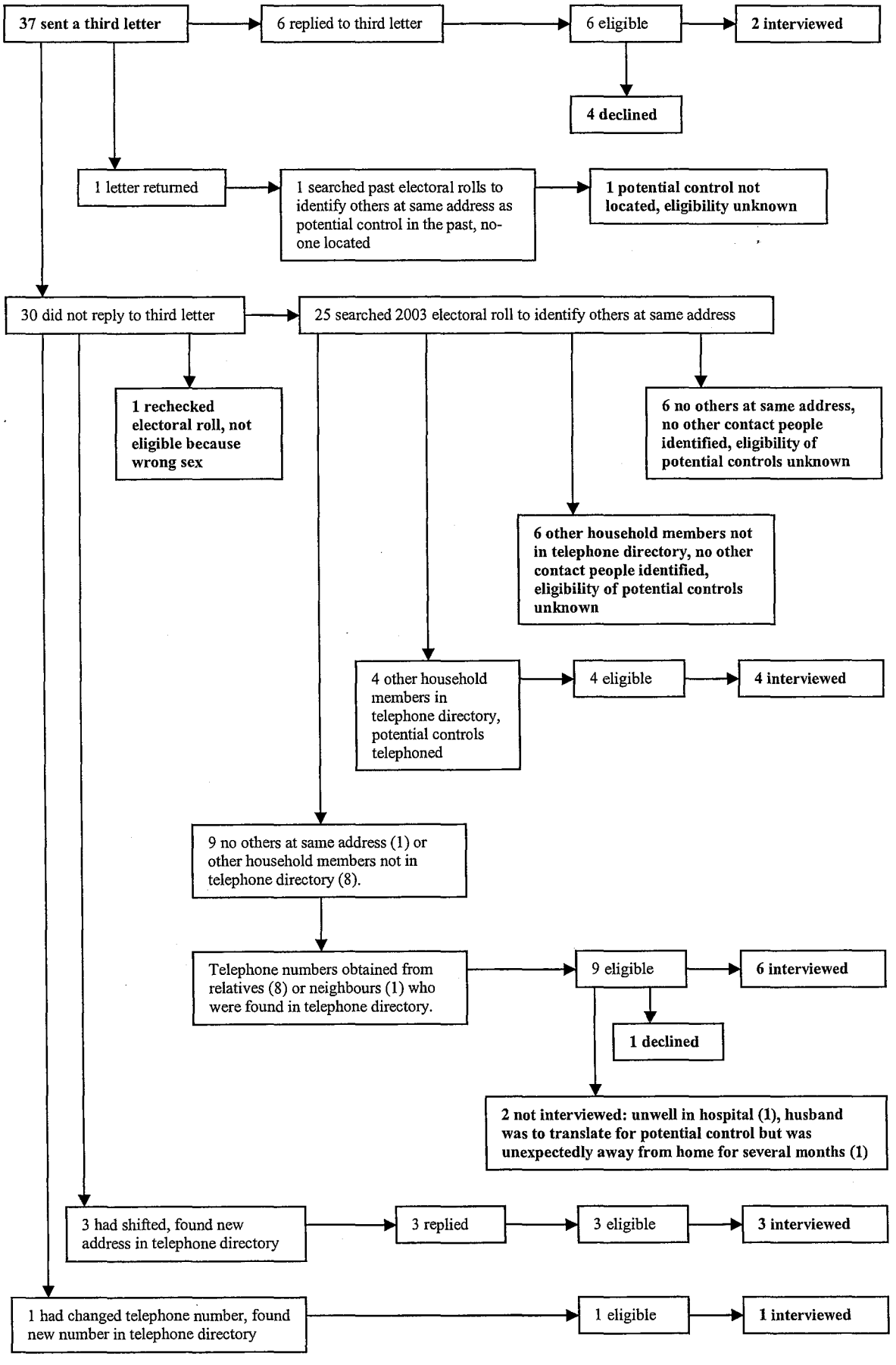

Figure 11.4 Responses of 37 potential controls to whom a third letter was sent

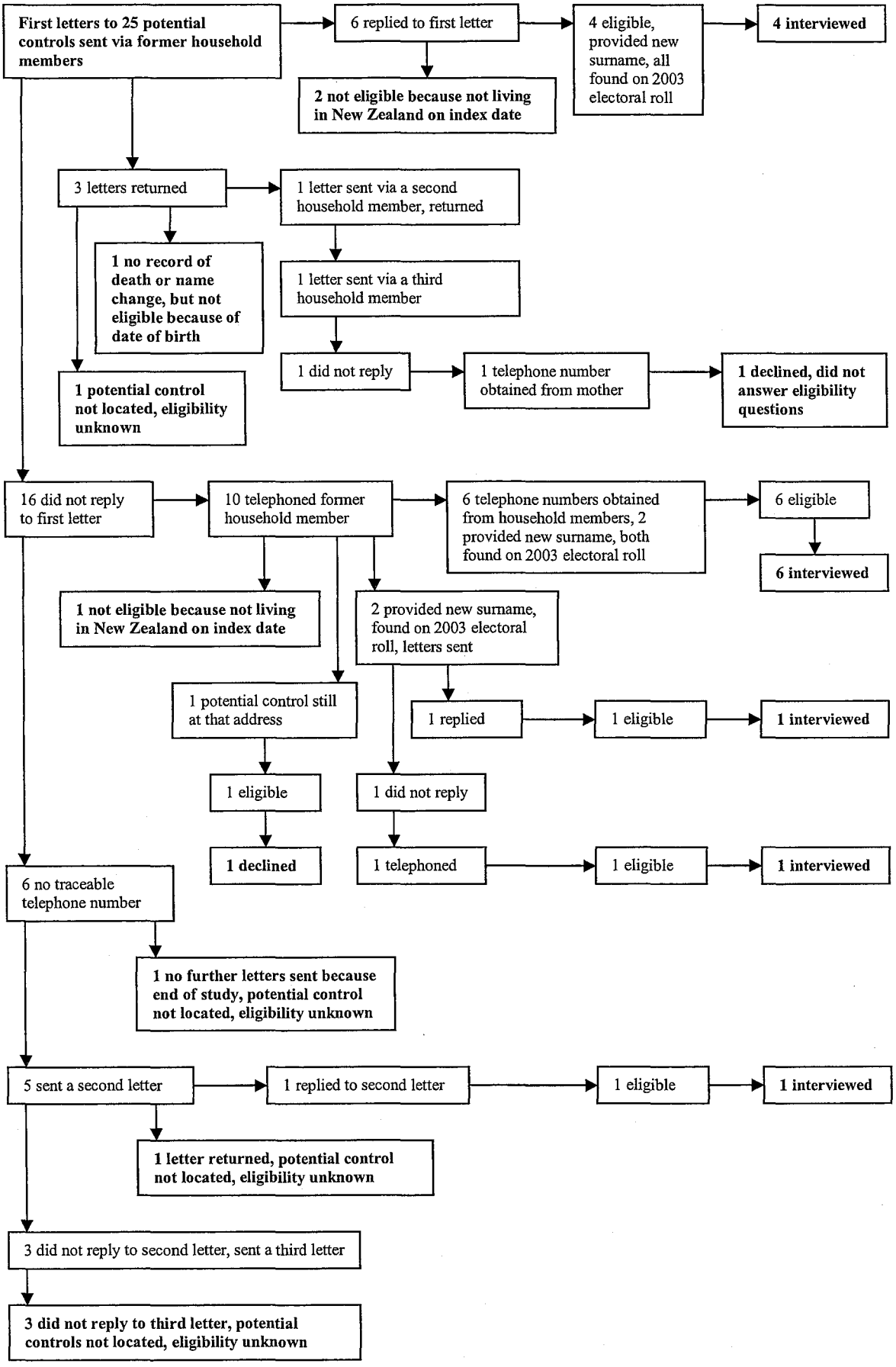

Figure 11.5 Responses of 25 potential controls to whom a letter was sent via relatives

Next of kin and controls who were interviewed

The eligibility and participation of the next of kin of cases and of the controls is summarised in Figure 11.6. The next of kin of 89 cases (89.9%) were interviewed, eight declined to participate, one initially consented but then could not be contacted, and for one case no replies were received from any of the three next of kin to whom letters were sent. Of the 462 potential controls selected from past electoral rolls, 21 were not eligible for inclusion in the study: 12 were the wrong age (three of whom died after the index date), five were the wrong sex, and four were not living in New Zealand on the index date. The eligibility status of 55 potential controls was not established: 15 died after the index date (including one man who died soon after a letter was sent to him) and were of an eligible age but it was not known whether they were living in New Zealand on the index date, 14 did not respond to letters of invitation, three declined to participate and to answer eligibility questions, and a total of 23 were not traced. Of the latter group, no postal address was found for 12, letters to six were returned ("gone, no forwarding address"), and no reply was received from five to whom letters were sent via former household members. A search of Births, Deaths, and Marriages records found no evidence that any of these 23 people had changed their names or died in New Zealand. The remaining 386 potential controls were eligible to be interviewed, but 28 did not wish to participate (one man initially consented, but cancelled the interview following the sudden death of his wife), one person was in hospital and too ill to be interviewed, and one woman agreed to be interviewed if her husband was able to act as her translator but he was subsequently away from home for several months. Hence, the response rate of potential controls lay between 80.7% (356 of 441) and 92.2% (356 of 386), since it is unlikely that everyone for whom eligibility status was not determined would have been eligible.

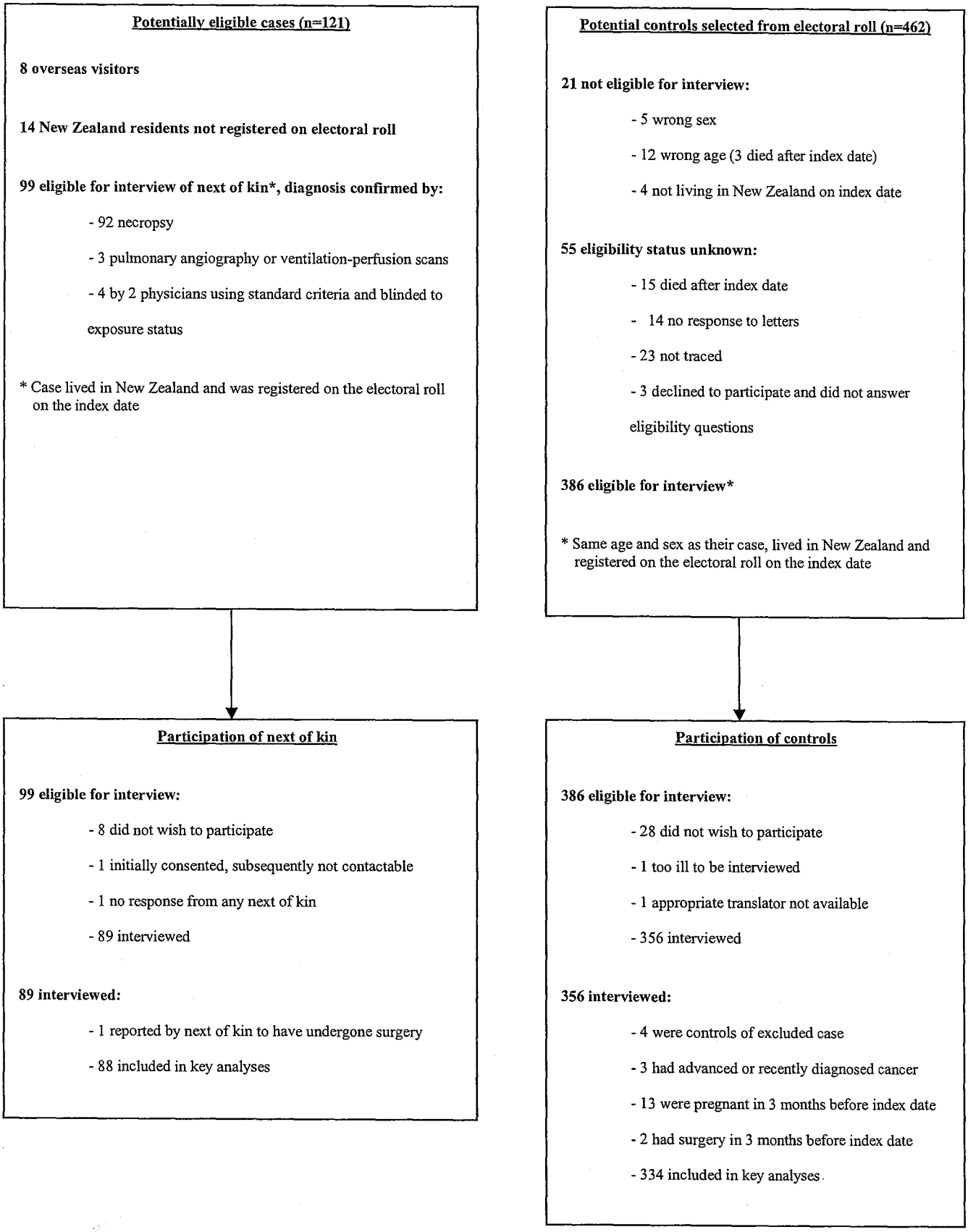

Figure 11.6 Eligibility and participation of controls and next of kin of cases

Cases and controls included in the key analyses

One case was reported by relatives to have undergone surgery following major injury in the three months before the index date. Although the reported surgery was not confirmed by his hospital or necropsy records (the injury was), this man was excluded from the key analyses because comparable sources of information were not available for the controls who stated that they had undergone surgery. Of the 356 controls who were interviewed, four were excluded from the key analyses because they were matched to the excluded case. A further 18 were excluded because they had conditions for which cases had been excluded: 13 were pregnant and two underwent surgery in the three months before the index date, while three had disseminated cancer or had been diagnosed with a malignancy (other than localised malignant melanoma) in the five years before the index date. Several other subjects who had reportedly been treated for cancer before the index date were not excluded from the key analyses as their disease appeared to have been cured. These cancers included localised malignant melanoma (one case, five controls), cervical cancer (two controls, both treated 10 years earlier — one with cone biopsy, the other with hysterectomy), ovarian cancer (one control, oophorectomy 40 years earlier when 12 years old), leukaemia (one control, treated 23 years earlier), and a malignant polyp of the colon (one case, excised seven years earlier). Hence, the key analyses were based on 88 cases and 334 controls.

11.1.2 Characteristics of cases and controls

The demographic characteristics of cases and controls are shown in Table 11.1. Of the 88 cases, 30 were male and 58 were female. The female cases were younger than the male (median ages 50.8 years and 42.6 years respectively). Cases spent fewer years at secondary school than controls and were less likely to have obtained a qualification after leaving school. Seven cases, but no controls, had attended special classes for people with intellectual disabilities. Cases were more likely than controls to belong to the lowest socio-economic group, although in univariate matched analyses people in the lowest socio-economic category did not have a significantly elevated risk of fatal pulmonary embolism when compared with those in the highest category (1.3 [95% CI 0.4 – 3.9]). The prioritised ethnic group of subjects did not differ appreciably between the case and control groups. Nine cases and 28 controls were identified as belonging to the Maori ethnic group. Of these, six cases and nine controls were also reported to belong to the New Zealand European or Other European ethnic groups (Tables 11.2 and

11.3). Of the three cases and 19 controls who were identified as belonging solely to the Maori ethnic group, all three cases and 16 of the controls were reported to have some European ancestry.

Table 11.1 Demographic characteristics of cases and controls

Characteristic	Cases (n=88)	Controls (n=334)*
Sex (number [%])		
Male	30 (34.1)	120 (35.9)
Female	58 (65.9)	214 (64.1)
Age (years, median)		
All	45.5	47.1
Male	50.8	50.4
Female	42.6	43.0
Years of secondary schooling		
None	3 (3.4)	8 (2.4)
1 – 2	18 (20.5)	57 (17.1)
3 – 4	43 (48.9)	202 (60.5)
≥ 5	13 (14.8)	67 (20.1)
Attended special education classes because of intellectual disability	7 (8.0)	-
Unknown	3 (3.4)	-
Did not answer question	1 (1.1)	-
Highest qualification obtained after leaving school		
None	53 (60.2)	154 (46.1)
Trade or technical certificate or diploma	16 (18.2)	83 (24.9)
Nursing certificate or diploma	4 (4.5)	18 (5.4)
Teaching certificate or diploma	4 (4.5)	12 (3.6)
University certificate or diploma	-	5 (1.5)
Bachelors degree	6 (6.8)	30 (9.0)
Post-graduate certificate or diploma	-	11 (3.3)
Post-graduate degree	1 (1.1)	6 (1.8)
Other	4 (4.5)	15 (4.5)
Socio-economic group (number [%])		
1 (highest)	5 (5.7)	18 (5.4)
2	8 (9.1)	32 (9.6)
3	27 (30.7)	119 (35.6)
4	18 (20.5)	82 (24.6)
5	9 (10.2)	43 (12.9)
6	19 (21.6)	39 (11.7)
Did not answer question about employment	2 (2.3)	1 (0.3)

Characteristic	Cases (n=88)	Controls (n=334)*
Prioritised ethnic group (number [%])		
European	76 (86.4)	295 (88.3)
Maori	9 (10.2)	28 (8.4)
Pacific Islands	3 (3.4)	4 (1.2)
Asian	-	4 (1.2)
Other	-	1 (0.3)
Did not answer question	-	2 (0.6)

* 18 controls are excluded: three had a history of cancer, two had surgery, and 13 were pregnant in the three months before the index date.

Table 11.2 Reported ancestry of cases who were reported to belong to the Maori ethnic group

Reported ancestry	**Reported ethnic group**	
	Maori only	Maori and European
Maori only	-	-
Maori and European	3	6

Table 11.3 Reported ancestry of controls who were reported to belong to the Maori ethnic group

Reported ancestry	**Reported ethnic group**	
	Maori only	Maori and European
Maori only	3	-
Maori and European	16	9

Other characteristics of cases and controls are shown in Table 11.4. Cases were more likely than controls to have a history of venous thromboembolism, to be obese, and to be nulliparous. In the three months before the index date, cases were also more likely than controls to have been immobilised for a prolonged period (confined to bed or a wheelchair for more than a week), to have been admitted to hospital owing to a medical condition, and to have taken oral contraceptives or antipsychotic drugs. Five of the cases and one of the controls who were admitted to hospital were also immobilised for a prolonged period.

Cases and controls had similar rates of smoking, of regular aspirin use, and of hormone replacement therapy during the same period. One case, and no controls, had systemic lupus erythematosus. Three cases, but no controls, had been told that they had a blood disorder which increased their chances of developing venous thromboembolism. Only one subject (a case) was reported to be taking an anticoagulant (warfarin). Comparable proportions of cases and controls had a history of varicose veins and a family history of venous thromboembolism. None of the cases or controls had been diagnosed with inflammatory bowel disease. Although female cases were more likely than controls to have taken oral contraceptives in the three months before the index date, the proportion of cases who had ever used this method of contraception before the index date was smaller that the proportion of controls who were ever users. Similarly, cases were less likely to have ever taken hormone replacement therapy and to have been diagnosed with hypertension during pregnancy.

In univariate matched analyses, statistically significant elevated risks of fatal pulmonary embolism were found for a history of venous thromboembolism (odds ratio 9.2 [95% CI 3.6 – 23.8]), BMI $\geq$ 30 kg/m^2 compared with BMI 20 – 24.9 kg/m^2 (odds ratio 2.9 [95% CI 1.5 – 5.5]), prolonged immobility (odds ratio 9.5 [95% CI 2.5 – 36.3]), a hospital admission owing to a medical condition (odds ratio 7.9 [95% CI 2.4 – 26.1]), and current use of oral contraceptives (odds ratio 4.9 [95% CI 2.0 – 12.0]) and antipsychotic drugs (odds ratio 7.8 [95% CI 1.9 – 31.1]). These variables were all included in the final multivariate models.

Table 11.4 Other characteristics of cases and controls

Characteristic	Cases (n=88)	Controls (n=334)*	Matched unadjusted odds ratio (95% CI)
Reported history (number [%])			
Venous thromboembolism	16 (18.2)	9 (2.7)	9.2 (3.6 – 23.8)
Varicose veins	23 (26.1)	80 (24.0)	1.2 (0.7 – 2.1)
Clotting disorder	3 (3.4)	-	-
Systemic lupus erythematosus	1 (1.1)	-	-
Hypertension unrelated to pregnancy	9 (10.2)	32 (9.6)	-
Angina	3 (3.4)	8 (2.4)	-
Myocardial infarction	-	1 (0.3)	-
Stroke	1 (1.1)	4 (1.2)	-
Heart valve disease	-	4 (1.2)	-
Cardiac conduction disorders	1 (1.1)	2 (0.6)	-
Type I diabetes	1 (1.1)	1 (0.3)	-
Type II diabetes	1 (1.1)	5 (1.5)	-
Gestational diabetes only	1 (1.1)	1 (0.3)	-
Chronic renal failure	2 (2.3)	1 (0.3)	-
BMI (kg/m², number [%])†			
< 20	7 (8.0)	26 (7.8)	1.2 (0.5 – 3.1)
20 – 24.9	31 (35.2)	153 (45.8)	1.0
25 – 29.9	21 (23.9)	104 (31.1)	1.0 (0.5 – 1.9)
≥ 30	28 (31.8)	51 (15.3)	2.9 (1.5 – 5.5)
Did not answer question	1 (1.1)	-	-
Risk factors in 3 months before index date (number [%])			
Major fracture	-	3 (0.9)	-
Major injury	1 (1.1)	1 (0.3)	-
Prolonged immobility‡	8 (9.1)	3 (0.9)	9.5 (2.5 – 36.3)
Hospital admission owing to a medical condition	9 (10.2)	4 (1.2)	7.9 (2.4 – 26.1)
Smoking status in 3 months before index date (number [%])			
Never smoked	47 (53.4)	157 (47.0)	1.0
Smoker	27 (30.7)	97 (29.0)	1.1 (0.6 – 1.8)
Ex-smoker	14 (15.9)	80 (24.0)	0.6 (0.3 – 1.1)
Medication use in 3 months before index date			
Antipsychotic (number [% total])	6 (6.8)	3 (0.9)	7.8 (1.9 – 31.1)
Antidepressant (number [% total])	1 (1.1)	8 (2.4)	-
Aspirin (number [% total])	3 (3.4)	7 (2.1)	-
Oral contraceptives (number [% female])	22 (37.9)	41 (19.2)	4.9 (2.0 – 12.0)
Hormone replacement therapy (number [% female])	4 (6.9)	17 (7.9)	1.0 (0.3 – 3.1)

Characteristic	Cases (n=88)	Controls (n=334)*	Matched unadjusted odds ratio (95% CI)
Ever use of medications before index date (number [% female])			
Oral contraceptives	41 (70.7)	179 (83.6)	-
Hormone replacement therapy	5 (8.6)	30 (14.0)	-
Number of births (number [% female])			
0	22 (37.9)	47 (22.0)	-
1 – 2	20 (34.5)	82 (38.3)	-
3 – 4	11 (19.0)	69 (32.2)	-
5 – 6	2 (3.4)	10 (4.7)	-
> 6	3 (5.2)	6 (2.8)	-
Hypertension in pregnancy (number [% female])	3 (8.3)	23 (13.8)	-
Reported family history of venous thromboembolism (number [%])	10 (11.4)	38 (11.4)	-

* 18 controls are excluded: three had a history of cancer, two had surgery, and 13 were pregnant in the three months before the index date.
† Based on weight and height measurements when provided, otherwise the BMI category was assigned using narrative comments about weight in relation to height.
‡ Confined to bed or a wheelchair for more than a week. Two cases were confined to a wheelchair: one for 30 years and the other for 33 years.

11.1.3 Cases and controls who undertook long-distance air travel

Five cases and nine controls had undertaken at least one long-distance flight in the four weeks before the index date. The median ages of these cases and controls were 49 years and 52.5 years respectively. Table 11.5 shows the characteristics of the cases, as reported by next of kin. The characteristics of the controls who flew are shown in Table 11.6.

Table 11.5 Characteristics of cases who undertook long-distance air travel in the four weeks before the index date*

Case	Sex	Age (years)	History of venous thromboembolism	BMI (kg/m^2)†	Other risk factors for venous thromboembolism	Family history of venous thromboembolism
1	Female	47	No	35.5	Norethisterone Medroxyprogesterone acetate Tranexamic acid	No
2	Female	51	Pregnancy-related DVT	"Average weight in relation to height"	History of vein surgery, but husband did not think that she had varicose veins	1 cousin with deep vein thrombosis
3	Female	58	No	21.2	History of varicose veins	No
4	Male	36	No	"Slightly overweight in relation to height"	Nil	No
5	Male	49	No	30.7	Paraplegia 33 years	No

* Information obtained from next of kin interviews only.
† Estimated from weight and height reported by next of kin.

Table 11.6 Characteristics of controls who undertook long-distance air travel in the four weeks before the index date

Control	Sex	Age (years)	History of venous thromboembolism	BMI (kg/m^2)*	Other risk factors for venous thromboembolism	Family history of venous thromboembolism
1	Female	25	No	19.4	Oral contraceptive use	No
2	Female	32	No	32.7	Nil	2 sisters with deep vein thrombosis
3	Female	48	No	19.7	Hormone replacement therapy	No
4	Female	52	No	21.7	No	No
5	Female	57	No	30.8	No	No
6	Female	59	No	24.1	Hormone replacement therapy Varicose veins	No
7	Male	19	No	26.3	No	No
8	Male	54	No	25.0	No	No
9	Male	58	No	28.1	No	No

* Estimated from self-reported weight and height.

11.1.4 Long-distance air travel undertaken by cases and controls

Information about the long-distance air travel undertaken by the five cases (cases 1 – 5) was shown in Table 9.5 in Chapter 9. As this information was obtained from next of kin it can be included in the case-control study. Corresponding information about controls is shown in Table 11.7. Four of the nine controls had journeys of at least eight hours. One control was an international flight attendant and had at least 18 long-distance flights during the relevant four-week period. She routinely lay down for two or three hours on each flight of more than 10 hours' duration. Another control undertook four long-distance flights, all in business class. Only one other control travelled in business class. Five of the six remaining controls travelled twice in the four weeks. None of the controls reported taking hypnotic drugs immediately before or during the flight, and there were no additional controls who had undertaken domestic flights within a country other than New Zealand during the relevant period.

Hence, in summary, five cases and nine controls undertook at least one flight of more than three hours' duration in the four weeks before the index date. All five cases and four of the controls had journeys of more than eight hours' duration.

Table 11.7 Long-distance air travel undertaken by controls in the four weeks before the index date

Control	Number of long-distance journeys undertaken by air	Total duration of long-distance journey (duration of each leg)	Number (duration) of stops during journey	Class of travel	Aisle seat	Hypnotic use	Interval between end of flight and index date	Other comments
1	18 – 26	11 h, 55 m, twice 10 h, 35 m, twice 11 h, 20 m, twice 12 h, 45 m, twice 10 h, 45 m, once 11 h, 0 m, once 7 h, 35 m, twice 6 h, 25 m, twice 3 h, 30 m, 2 – 6 times 3 h, 0 m, 2 – 6 times	All flights non-stop	Not relevant	Not relevant	No	Flew regularly throughout four-week period	International flight attendant. During each flight of more than 10 hours had a 2 – 3 hour rest period during which she was able to lie down.
2	2	3 h, 30 m 3 h, 0 m	0 0	Economy Economy	Yes Yes	No No	11 days 7 days	

Control	Number of long-distance journeys undertaken by air	Total duration of long-distance journey (duration of each leg)	Number (duration) of stops during journey	Class of travel	Aisle seat	Hypnotic use	Interval between end of flight and index date	Other comments
3	4	11 h, 55 m	0	Business	Yes	No	26 days	The control's case had a history of venous thromboembolism
		5 h, 5m*	0	Business	No	No	21 days	
		6 h, 5 m*	0	Business	No	No	14 days	
		12 h, 30 m	0	Business	Yes	No	4 days	
4	1	3 h, 45 m	0	Business	No	No	2 days	The control's case had a history of venous thromboembolism
5	2	4 h, 0 m	0	Economy	No	No	17 days	Not in New Zealand on the index date / date of death of case
		3 h, 30 m	0	Economy	No	No	11 days	
6	2	11 h, 40 m	0	Economy	No	No	17 days	
		11 h, 0 m	0	Economy	No	No	11 days	
7	2	3 h, 0 m	0	Economy	No	No	21 days	
		3 h, 0 m	0	Economy	No	No	12 days	
8	2	14 h, 25 m (3 h 30 m, 10 h 55 m)	1 (2 h)	Economy	Not recalled	No	25 days	
		12 h, 15 m (9 h 20 m, 2 h 55 m)	1 (4 h)	Economy	Not recalled	No	15 days	
9	1	3 h, 45 m	0	Economy	Yes	No	23 days	Not in New Zealand on the index date, but returned before the date the case died

* Domestic flights within a country other than New Zealand.

Abbreviations used in the table h: hours, m: minutes.

11.1.5 Estimated relative risk of fatal pulmonary embolism in long-distance air travellers

The results of the key analyses are shown in Table 11.8. Taking those who had not flown as the reference group, the odds ratio (adjusted for a history of venous thromboembolism, for the BMI category, and for prolonged immobility, any hospital admission owing to a medical condition, oral contraceptive, or antipsychotic use in the three months before the index date) for a flight of at least three hours' duration was 1.8 (95% CI 0.5 – 7.1). For flight times of more than eight hours, the adjusted odds ratio was 7.9 (95% CI 1.1 – 55.1). Socio-economic status did not confound the association. When BMI as a continuous variable was entered into the multivariate model the adjusted odds ratio for a flight of more than eight hours' duration was 7.6 (95% CI 1.2 – 48.1).

Excluding controls who were not in New Zealand on the date of death of their case (n=2) had minimal impact on the results. The odds ratios (adjusted for a history of venous thromboembolism, for the BMI category, and for prolonged immobility, any hospital admission owing to a medical condition, oral contraceptive, or antipsychotic use in the three months before the index date) for air travel of at least three hours' and more than eight hours' duration were 1.9 (95% CI 0.5 – 7.5) and 7.9 (95% CI 1.1 – 55.1) respectively.

Similar point estimates were obtained when people with a history of venous thromboembolism, or of major injury or prolonged immobility in the three months before the index date were excluded from the analysis (Table 11.9). The odds ratio (adjusted for the BMI category and for any hospital admission owing to a medical condition, oral contraceptive, or antipsychotic use in the three months before the index date) for all air travel of more than eight hours was then 7.1 (95% CI 0.8 – 64.1).

Table 11.8 Long-distance air travel and fatal pulmonary embolism

Flight details	Cases	Controls	Matched unadjusted odds ratio (95% CI)	Matched adjusted odds ratio (95% CI)*	Matched adjusted odds ratio (95% CI)†
No long-distance flight	83	325	1.0	1.0	-
Air travel ≥ 3 hours	5	9	2.2 (0.7 – 6.8)	1.8 (0.5 – 7.1)	-
No long-distance flight	83	325	1.0	1.0	1.0
Air travel > 8 hours‡	5	4	6.0 (1.4 – 25.4)	7.9 (1.1 – 55.1)	7.6 (1.2 – 48.1)

* Adjusted for a history of venous thromboembolism, for the BMI category, and for prolonged immobility, any hospital admission owing to a medical condition, oral contraceptive, or antipsychotic use in the three months before the index date.
† Adjusted for a history of venous thromboembolism, for BMI as a continuous variable (using imputed values for missing data), and for prolonged immobility, any hospital admission owing to a medical condition, oral contraceptive, or antipsychotic use in the three months before the index date.
‡ Five controls who undertook air travel of eight hours or less are excluded from the analysis.

Table 11.9 Long-distance air travel and fatal pulmonary embolism, excluding people with a history of venous thromboembolism or of major injury or prolonged immobility in the three months before the index date

Flight details	Cases	Controls	Matched unadjusted odds ratio (95% CI)	Matched adjusted odds ratio (95% CI)*
No long-distance flight	62	230	1.0	1.0
Air travel ≥ 3 hours	3	7	1.6 (0.4 – 6.5)	1.1 (0.2 – 5.4)
No long-distance flight	62	230	1.0	1.0
Air travel > 8 hours†	3	3	5.0 (0.8 – 31.0)	7.1 (0.8 – 64.1)

* Adjusted for the BMI category, and for any hospital admission owing to a medical condition, oral contraceptive, or antipsychotic use in the three months before the index date.

† Four controls who undertook air travel of eight hours or less are excluded from the analysis.

11.1.6 Other risk factors for fatal pulmonary embolism

The estimated relative risks of fatal pulmonary embolism associated with other risk factors are shown in Table 11.10. People with a history of venous thromboembolism had a 10-fold increased risk of dying from pulmonary embolism when compared with people without such a history; the odds ratio (adjusted for air travel of more than eight hours, for the BMI category, and for prolonged immobility, any hospital admission owing to a medical condition, oral contraceptive, or antipsychotic use in the three months before the index date) was 10.6 (95% CI 3.7 – 31.0). People who were obese were more likely to die from pulmonary embolism than those with a normal BMI; the adjusted odds ratio for a BMI $\geq$ 30 kg/m^2, compared with a BMI of 20 – 24.9 kg/m^2, was 2.8 (95% CI 1.3 – 5.8). The adjusted odds ratios for prolonged immobility and for any admission to hospital owing to a medical condition in the three months before the index date were 2.4 (95% CI 0.4 – 14.6) and 11.5 (1.5 – 88.6) respectively. When compared with non-users, users of oral contraceptives in the three months before the index date had an increased risk of fatal pulmonary embolism; the adjusted odds ratio was 7.1 (95% CI 2.7 – 18.8). Antipsychotic use was also associated with an increased risk; the adjusted odds ratio was 8.4 (95% CI 1.7 – 42.0). No increased risks were observed for a reported history of varicose veins, a family history of venous thromboembolism, or for smoking or hormone replacement therapy in the three months before the index date. Very similar results were obtained when the odds ratios were adjusted for BMI as a continuous variable.

Table 11.10 Other risk factors and fatal pulmonary embolism

Risk factor	Cases (n=88)	Controls (n=334)	Matched adjusted odds ratio (95% CI)*	Matched adjusted odds ratio (95% CI)†
Reported history				
VTE	16	9	10.6 (3.7 – 31.0)	8.8 (3.1 – 25.4)
Risk factors in 3 months before index date				
Prolonged immobility	8	3	2.4 (0.4 – 14.6)	2.4 (0.4 – 14.2)
Hospital admission owing to a medical condition	9	4	11.5 (1.5 – 88.6)	11.2 (1.6 – 78.1)
Medication use in 3 months before index date				
Antipsychotic	6	3	8.4 (1.7 – 42.0)	7.4 (1.6 – 34.6)
Oral contraceptives	22	41	7.1 (2.7 – 18.8)	5.9 (2.2 – 15.4)
BMI as a categorical variable				
< 20	7	26	0.7 (0.2 – 2.2)	-
20 – 24.9	31	153	1.0	-
25 – 29.9	21	104	1.0 (0.5 – 2.0)	-
≥ 30	28	51	2.8 (1.3 – 5.8)	-
Did not answer question	1	0	-	
BMI as a continuous variable‡	88	334		1.08 (1.02 – 1.14)

* Variables included in the model were long-distance air travel of more than eight hours, a history of venous thromboembolism, the BMI category (four categories), and prolonged immobility, any hospital admission owing to a medical condition, oral contraceptive, and antipsychotic use in the three months before the index date.

† Variables included in the model were long-distance air travel of more than eight hours, a history of venous thromboembolism, BMI as a continuous variable, and prolonged immobility, any hospital admission owing to a medical condition, oral contraceptive, and antipsychotic use in the three months before the index date.

‡ Missing values imputed.

11.2 DISCUSSION

As discussed earlier, the number of cases of fatal pulmonary embolism was inevitably restricted by the relative rarity of the condition and the size of the New Zealand population. Hence, there were only 121 deaths over an 11-year period among people aged 15 – 59 years in which pulmonary embolism was considered the underlying cause. Of these, 98 were identified as being eligible for inclusion in the case-control study and the next of kin of 88 were interviewed. The precision of the estimates of relative risk was accordingly restricted, as shown by the wide 95% confidence intervals. Nevertheless, people who had undertaken air travel of more than eight hours' duration had a significant eight-fold increased risk of fatal pulmonary embolism in the subsequent four weeks when compared with people who had not undertaken any long-distance flights. This is consistent with the findings of the descriptive study from which, allowing for a "healthy traveller" effect, a six-fold increase in risk can be estimated. The relative risk estimate for flights of at least three hours' duration, although not significant, was also elevated.

11.2.1 Potential sources of bias to be considered

Ascertainment of cases

As has already been discussed in previous chapters, in this population-based research it was possible to identify all deaths that occurred in New Zealand during the study period for which pulmonary embolism was considered the underlying cause. Because fatal events were studied, and because the deaths occurred before widespread media publicity about a possible link between long-distance flights and venous thromboembolism, diagnostic and referral biases are very unlikely in this study. Moreover, even if a referral bias had occurred, with individuals who developed symptoms of venous thromboembolism following a flight being more likely to be referred promptly for investigation and treatment (possibly preventing some deaths), this should have led to an underestimate of the association between air travel and fatal pulmonary embolism.

The response rate of next of kin was high (89.9%). However, to explore the possible impact that the omission of the 10 eligible cases might have had on the estimates of relative risk, a sensitivity analysis was undertaken. It was assumed that none of the 10 cases had undertaken long-distance air travel in the four weeks before the index date

and that one of their 40 controls had undertaken a flight of at least three hours' duration, but none had flown for more than eight hours (based on the observed proportions of controls exposed to flights of these durations). In this matched analysis, based on 98 cases and 374 controls, the unadjusted odds ratios for a flight of at least three hours' duration and air travel of more than eight hours were 2.0 (95%CI 0.6 – 5.9) and 4.5 (95% CI 1.2 – 17.1) respectively. Hence, the failure to include all eligible cases could not fully explain the observed association between air travel of more than eight hours' duration and fatal pulmonary embolism.

Selection of controls

Controls were selected using the same criteria as the cases, namely that they had to have been living in New Zealand, and registered on the electoral roll, on the index date. Moreover, electoral rolls from the index (or adjacent) years, rather than the most recent roll, were used to select potential controls, thus ensuring that the controls did indeed come from the population that gave rise to the cases. The response rate of potential controls was similar to that of cases and lay between 80.7% and 92.2%, since it is unlikely that everyone for whom eligibility status was not determined would have been eligible.

It is possible that potential controls who died after the index date, or could not be traced or contacted, were less likely to have undertaken long-distance air travel because of illness or because they belonged to a lower socio-economic group. For instance, it is clear that some of the potential participants who died after the index date were suffering from serious medical conditions that were present before the index date (see Table 10.1 in the previous chapter). The effect of any selection bias arising from the exclusion of such people, and the failure to trace other potential controls, should have been to weaken the association between air travel and pulmonary embolism. It appears, however, that the control group gave a reliable estimate of exposure in the population that gave rise to the cases, since the estimated number of arrivals based on the proportion of exposed controls was similar to the number of arrivals identified in official migration data.

Recall bias

A potential source of bias in the present study is the use of proxy respondents for cases, but not for controls. The reasons for interviewing the controls, rather than their next of kin, were reviewed in the previous chapter. Several measures were employed to minimise any differential recall or knowledge between controls and the next of kin of cases. First, a life events calendar was sent to each participant and used during the interview to locate events in time as described in the previous chapter. Second, next of kin and controls were asked to check passports and other records before they answered questions about international air travel. Many cases and controls had never left New Zealand and hence there was no need to refer to records. It was also interesting to observe that for those who had undertaken one "trip of a life-time" or a "big overseas experience", and for those who had travelled rarely, the next of kin and controls appeared to have no difficulty in correctly recalling whether long-distance air travel had been undertaken during the relevant four-week period. Similarly, accurate recall did not appear to be difficult in situations where cases and controls undertook at least one international trip annually for work or family-related reasons, because travel was often undertaken at the same time each year. These people also appeared to habitually travel in the same class, request certain seating positions, and to use or not use hypnotics. The third measure to minimise differences in the information obtained for cases and controls was that the dates of hospital admissions were verified for both groups. Hence, it was possible to confirm admissions for surgery, major injury, pregnancy, and medical conditions during the three months before the index date. Finally, wherever possible, the next of kin with whom the cases had lived were interviewed and the reliability of the information provided by these relatives was tested by comparing it with data from other sources.

Comparison of information obtained from next of kin with data from other sources

All long-distance flights reported by next of kin were confirmed by medical and death records and existing records did not identify any flights that were not also reported by next of kin. The dependability of information provided by next of kin about other risk factors for venous thromboembolism was also examined by comparing it with information from existing records (Tables 11.11 – 11.15). From Table 11.11 it appears that the next of kin were a reliable source of information about the use of oral contraceptives and antipsychotic drugs in the three months before the index date.

Further support for this view is provided by the adjusted odds ratios for these risk factors (as reported in Table 11.10) which are remarkably consistent with the findings of the case-control study described in Chapters 4 – 6 and with the results of other research (Walker et al. 1997; Zornberg and Jick 2000; Vandenbroucke et al. 2001). In contrast, it appears that the next of kin were not a good source of information about hormone replacement therapy and that some users were misclassified as non-users. This might be one explanation for the absence of an association between hormone replacement therapy and fatal pulmonary embolism where one would be expected. Alternatively, the observed socio-economic and educational differences between cases and controls (more cases in the lower socio-economic groups and fewer with tertiary education) may also have played a part — since hormone replacement therapy was used more often in the 1990s by New Zealand women with higher levels of education and income (North and Sharples 2001). It is also possible that while the medical records indicated that hormone replacement therapy was prescribed, the next of kin knew that the prescription was not taken to the pharmacy, or that the dispensed medication was not taken.

Next of kin identified more cases who had been immobilised for a prolonged period in the three months before the index date than did existing records. This is not surprising since it is possible to be confined to bed or a chair for more than a week without such immobility being explicitly recorded in medical records.

Table 11.11 Presence of risk factors for venous thromboembolism in the three months before the index date, comparison of information obtained from existing records and from next of kin

Information from existing records	Information from next of kin			
	Yes	**No**	**Don't know**	**Other**
Taking oral contraceptive (n=58)*				
Yes	17	2	1	1 ("minipill")
No	-	29	3	-
Possibly	1	-	-	-
Progestogen-only pill	2	-	-	-
Depo medroxyprogesterone acetate	1	-	-	-
General practice records lost, no reference to contraceptive methods in hospital records	1	-	-	-
Taking hormone replacement therapy (n=58)†				
Yes	4	4	1	-
No	-	48	1	-
Taking antipsychotic medication (n=88)‡				
Yes	6	1	2	1 ("something to stop him drinking")
No	-	78	-	
Prolonged immobility (n=88)				
Yes	3	-	-	-
No	1	80	-	-
Record of hospital admission and reduced mobility	4	-	-	-

* This information was obtained in response to a specific question about the use of oral contraceptives in the three months before the index date.
† This information was obtained in response to a specific question about hormone replacement therapy in the three months before the index date.
‡ This information was obtained in response to questions about the use of medications (other than oral contraceptives and hormone replacement therapy) in the three months before the index date.

Table 11.12 compares the data obtained from existing records with the information provided by next of kin about previous venous thromboembolism events. As was explained in the previous chapter, all those who had a history of treatment for superficial, deep, or unspecified venous thrombosis, or for pulmonary embolism, were classified as having a history of venous thromboembolism. Using this approach, only two cases who had a recorded history of deep vein thrombosis or pulmonary embolism were not identified by next of kin as having a history of venous thromboembolism. Perhaps not surprisingly, since it is a less serious event, only seven of the 17 cases with a recorded history of superficial venous thrombosis were reported by next of kin to have had a blood clot in the legs. The effect of classifying some cases of superficial venous thrombosis as having a history of venous thromboembolism appears to have had little impact on the estimates of relative risk of fatal pulmonary embolism in people with a history of venous thromboembolism; the adjusted odds ratios for a history of venous thromboembolism in the present study were consistent with previous research (Samama and the Sirius Study Group 2000). This classification did, however, contribute to a loss of power in analyses from which people with a history of venous thromboembolism were excluded.

Table 11.13 compares the data obtained from existing records with the information provided by next of kin about a family history of venous thromboembolism. The next of kin identified more cases with a family history of venous thromboembolism than did existing records. This is not unexpected since family members are likely to possess more complete information. It is surprising however, that the adjusted odds ratio for a family history of venous thromboembolism was not elevated.

Table 11.12 History of venous thromboembolism event, comparison of information obtained from existing records and from next of kin

Information from existing records	**Information from next of kin**					
History of venous thromboembolism event	Blood clot in leg, not known whether superficial or deep	Blood clot in leg, in superficial veins only	Blood clot in leg, in deep veins	Pulmonary embolism, with or without venous thrombosis	Don't know whether had blood clot, no pulmonary embolism	No blood clot or pulmonary embolism
Superficial venous thrombosis only	1*	4*	2*	-	2	8
Deep vein thrombosis, no pulmonary embolism	2*	-	3*	-	1	-
Pulmonary embolism, with or without venous thrombosis	2*	1*	-	-	-	1
No venous thrombosis or pulmonary embolism	-	1*	-	-	-	60

* These cases were classified as having a history of venous thromboembolism in the case-control study.

Table 11.13 Family history of venous thromboembolism, comparison of information obtained from existing records and from next of kin

Information from existing records	**Information from next of kin**	
Family history of venous thromboembolism	Yes	No
Yes	3	2
No	7	76

In Tables 11.14 and 11.15, the information obtained from necropsy reports (or other records in the absence of such information) about BMI is compared with information provided by next of kin. Table 11.14 compares information about the 61 cases for whom weight and height estimates were provided by next of kin, while Table 11.15 compares information about the 26 cases for whom the BMI category was assigned using the narrative comments made by next of kin about weight in relation to height. The case whose relative did not wish to provide weight information was observed at necropsy to be a "normal weight". As can be seen in the tables, some pathologists did not measure the weight and height of cases and instead simply made comments, some of which were not particularly informative about body size. For example, some of the cases who were described by pathologists as being "well-nourished" were reported by their relative to be underweight, while others were reported to be a normal weight, overweight, or even obese.

Table 11.14 BMI calculated from weight and height reported by next of kin of 61 cases, compared with information obtained from existing records

BMI category based on information from existing records	**BMI category calculated from weight and height reported by next of kin**			
	Underweight (n=3)	Normal weight (n=22)	Overweight (n=13)	Obese (n=23)
BMI calculated from weight and height measured at necropsy (n=35)				
Normal weight	3	8		
Overweight		4	1	2
Obese		3	5	9
Comments at necropsy (n=21)				
"Diminutive"				1
"Lean"		1		
"Medium build"		1		
"Well-nourished"		1	1	1
"Solid build"		1		
"Very heavily built"				1
"Overweight"				1
"Slightly obese"			1	
"Moderate central obesity"		1		
"Moderate obesity"			2	2
"Obese"		1	1	2
"Hugely or markedly obese"				2
No information from necropsy, but information from other records (n=1)				
Obese				1
No information from necropsy, or from other records (n=2)		1	1	
No necropsy, but information from other records (n=2)				
Obese			1	1

BMI categories in table Underweight: < 20.0 kg/m², normal weight: 20.0 – 24.9 kg/m², overweight: 25.0 – 29.9 kg/m², obese: ≥ 30.0 kg/m².

Table 11.15 BMI category reported by next of kin of 26 cases, compared with information obtained from existing records

BMI category based on information from existing records	Next of kin reported that for height case was:			
	Underweight (n=4)	About right weight (n=9)	Overweight (n=13)	
			No additional comments (n=8)	Additional comments indicated was obese (n=5)
BMI calculated from weight and height at necropsy (n=10)				
Normal weight		1		
Overweight		1	1	
Obese		1	3	3
BMI category assigned from weight at necropsy (n=1)				
Obese			1	
Comments at necropsy (n=10)				
"Average build"	1			
"Well-nourished"	1	1		
"Moderately heavily built"		1		
"Moderately overweight"		1		
"Tall, rather obese"		1		
"Obese"		1		1
"Grossly obese"			1	1
No information from necropsy, but information from other records (n=2)				
Underweight	1			
Overweight	1			
No necropsy, but information from other records (n=2)				
Overweight		1	1	
No necropsy, and no information from other records (n=1)			1	

BMI categories in table Underweight: < 20.0 kg/m², normal weight: 20.0 – 24.9 kg/m², overweight: 25.0 – 29.9 kg/m², obese: ≥ 30.0 kg/m².

To obtain an estimate of BMI for cases whose weight or height was not measured at necropsy, as well as those who did not have a necropsy, other records were searched to find the most recent weight and height measurements. If a measurement was found for only one of these variables, then sex and age-specific data from the 1997 New Zealand National Nutrition Survey (Russell et al. 1999) were used to replace the missing variable. For instance, if there was a record of weight, but not height, for a 21 year old female case, then the mean height of women aged 19 – 24 years in the National Nutrition Survey was used to estimate BMI. If there was some indication in the records that the woman was short or tall, then the lower and upper quartile values respectively were used instead of the mean.

This investigation revealed that there were 40 cases for whom the BMI category derived from next of kin information differed from that derived from existing records; the BMI of 37 of these cases was underestimated by their relatives (Table 11.16). Some of this apparent misclassification can be attributed to the fact that next of kin were only presented with three possible narrative responses ("about right", "overweight", or "underweight") to the question about weight in relation to height (although they were given the opportunity to make additional comments). Moreover, several cases only just scraped into a BMI higher category. These issues aside, it appears that many next of kin simply misjudged the weight and height measurements of their relative such that the BMI was underestimated. This would be a problem if controls had accurately reported their weight and height. However systematic underestimation of self-reported weight has been observed (Spencer et al. 2002), and hence it is possible that the BMIs of the controls were also underestimated.

Nonetheless, it was decided to re-examine the association between long-distance air travel and fatal pulmonary embolism using a conservative scenario in which the BMI category of the above 40 cases was reclassified based on information from existing records, as shown in Table 11.16. In addition, the case whose next of kin did not answer the weight questions was classified as "normal weight" on the basis of existing data. In this analysis, the BMI categories of the remaining 47 cases and those of the controls remained unchanged. Following the reclassification, only one case was left in the underweight category so the underweight and normal weight categories were

combined to form the reference category for BMI. The odds ratio (adjusted for a history of venous thromboembolism, for the BMI category ["underweight / normal", "overweight", "obese"], and for prolonged immobility, any hospital admission owing to a medical condition, oral contraceptive, or antipsychotic use in the three months before the index date) for a flight of at least three hours' duration was 1.1 (95% CI 0.2 – 5.0) compared with the original estimate of 1.8 (95% CI 0.5 – 7.1). For flight times of more than eight hours, the adjusted odds ratio was 5.5 (95% CI 0.6 – 50.8) as compared with 7.9 (95% CI 1.1 – 55.1) in the original analysis. A second sensitivity analysis was undertaken in which BMI was treated as a continuous variable. After correcting for the misclassification discussed above, the odds ratio (adjusted for a history of venous thromboembolism, for BMI as a continuous variable, and for prolonged immobility, any hospital admission owing to a medical condition, oral contraceptive, or antipsychotic use in the three months before the index date) for air travel of more than eight hours was 6.1 (95% 0.9 – 42.5). Thus, the misclassification of BMI among the cases (assuming no misclassification among controls) did not have an appreciable impact on the estimated risk of fatal pulmonary embolism in people who had undertaken long-distance air travel.

Table 11.16 Reassignment of BMI category for sensitivity analysis

BMI category based on information from next of kin*	Reassigned BMI category based on information from existing records†	Number of cases (n=41)
Underweight‡	Normal weight	5
	Overweight	1
Normal weight§	Overweight	7
	Obese	8
Overweight‖	Obese	16
Obese¶	Overweight	3
Next of kin did not answer questions about weight	Normal weight	1

* The BMI was calculated from weight and height estimates if provided, otherwise the BMI category was assigned based on the response to the question about weight in relation to height.
† Necropsy, hospital, general practice, family planning, and mental health records.
‡ BMI < 20.0 kg/m²
§ BMI 20.0 – 24.9 kg/m²
‖ BMI 25.0 – 29.9 kg/m²
¶ BMI ≥ 30.0 kg/m²

In summary then, recall bias seems an unlikely explanation for the observed association between long-distance air travel and the risk of fatal pulmonary embolism for several reasons. First, the use of passports and other records to confirm travel details helped to ensure that accurate information about air travel by cases and controls as far back as 1990 was obtained. Second, since hospital admissions were verified, it was possible to confirm the presence of several major risk factors for venous thromboembolism in the three months before the index date for both cases and controls. Third, next of kin appeared to be a reliable source of information about most other risk factors for venous thromboembolism. Fourth, although next of kin tended to underestimate the body size of their relative, sensitivity analyses showed that this had only a small effect on the observed association between long-distance air travel and fatal pulmonary embolism. Finally, the relative risk estimates for most established risk factors for venous thromboembolism in the present study were in keeping with the results of earlier research (Rosendaal 1999a; Goldhaber 2004), which would tend to suggest that recall bias did not play a meaningful role.

Interviewer bias

Obviously the nurse interviewer and I always knew whether we were interviewing a next of kin or a control, however the administration of a standardised computer-assisted telephone interview and ongoing supervision of the nurse interviewer minimised any potential for interviewer bias. We both undertook interviews with similar proportions of next of kin and of controls. Next of kin and controls were not informed of the study hypothesis, nor were the controls told about the condition being studied until their interview was completed. The enquiries about air travel were made following questions about medical conditions and medicine use, so it is unlikely that participants would have identified this as the primary exposure of interest and modified their responses.

11.2.2 Potential confounding

Controls were matched to cases by sex, individual year of age, and electorate, and a matched analysis was undertaken. Hence, the observed association between air travel of more than eight hours' duration is not due to confounding by sex, age, or proximity to an international airport. Although there were temporal changes in travel patterns during the study period, such changes cannot explain the association because controls were asked about air travel during the same calendar period as their cases.

Concomitant drug use is also an unlikely explanation as the relative risk estimates were adjusted for the use of oral contraceptives and antipsychotic drugs in the three months before the index date. Since the use of aspirin did not differ between cases and controls, it was not included in the final model. Hormone replacement therapy was also excluded from the final model as its use by cases (as reported by next of kin) did not differ from controls. The use of anticoagulant drugs was not of concern as only one subject was taking one of these drugs.

The relative risk estimates were also adjusted for BMI. As discussed above, it appears that the BMI category of a substantial proportion of the cases was misclassified. While the significant association between air travel and fatal pulmonary embolism remained when the BMI of the cases was reclassified correctly, it is not possible to rule out some residual confounding by BMI since it is not known to what degree the BMI of the controls was also misclassified.

Confounding by an underlying medical condition is unlikely since individuals with cancer or a history of surgery or pregnancy in the three months before the index date were excluded, and the relative risk estimates were adjusted for a history of venous thromboembolism, and for prolonged immobility, and any hospital admissions owing to a medical condition in the three months before the index date. It was decided to adjust for a history of venous thromboembolism, a hospital admission, and prolonged immobility rather than excluding subjects with these risk factors, to avoid the loss of power inherent in excluding subjects. Because the study was confined to cases that occurred before widespread publicity about a possible link between air travel and venous thromboembolism, there was no reason to suppose that people with a history of venous thromboembolism would have been less likely to undertake long-distance air travel than those without such a history. Hence, the inclusion of these people should not have introduced a bias. While it is conceivable that people who had been unwell in the three months before the index date might have been less likely to travel during the four weeks leading up to the index date, the point estimate that was obtained when such people (and those with a history of venous thromboembolism) were excluded was identical to that obtained when adjustment was undertaken for the presence of these risk factors.

11.2.3 Consistency with other studies

The finding in the present study that long-distance flight is associated with a increased risk of fatal pulmonary embolism is consistent with most previous analytical studies of non-fatal events (Ferrari et al. 1999; Arya and Cohen 2003; Martinelli et al. 2003; Schwarz et al. 2003; Becker et al. 2006; Cannegieter et al. 2006), although a few studies found no such increase (Kraaijenhagen et al. 2000; Hosoi et al. 2002; ten Wolde et al. 2003).

Sensitivity analyses suggested that the omission of 10 eligible cases and the misclassification of BMI, might have led to a slight overestimation of the true risk of fatal pulmonary embolism in recent air travellers. Conversely, other factors may have operated to produce a conservative estimate of risk. Nonetheless, the magnitude of the increased risk in the present research is similar to that initially reported in a population-based case-control study in the Netherlands and a record-linkage case-crossover study in Western Australia (Rosendaal 2002; Kelman et al. 2003). In the first MEGA study analysis, based on 829 cases and 829 controls, air travel in the two months before the index date was associated with a six-fold increased risk of non-fatal venous thromboembolism (odds ratio 5.8 [95% CI 2.0 – 16.6]) (Rosendaal 2002). This risk was attenuated in a later analysis based on 1,906 cases and 1,906 controls (odds ratio 3.0 [95% CI 1.3 – 7.1]) (Cannegieter et al. 2006), although confounding by factors such as BMI and the factor V Leiden mutation was not accounted for in this estimate. Moreover, although the researchers reported that the risk of venous thromboembolism was greatest during the first week after a flight, they only reported odds ratios for an eight-week period following travel. It is possible, therefore, that the true relative risk of flight-related venous thromboembolism was underestimated. The Western Australian investigators also reported a declining risk with increasing time since travel. In their first analysis, the relative risks of venous thromboembolism in the first and second weeks after flying were 5.61 (95% CI 3.94 – 7.97) and 2.63 (95% CI 1.55 – 4.45) respectively, and the risk was not elevated after a 14-day period. In their later analysis, which included both Australian and non-Australian citizens and accounted for ageing over the study period and time spent outside Australia, there was a 30-fold increased risk that a venous thromboembolic event would be triggered on the day of an international flight (relative risk 29.8 [95% CI 22.4 – 37.3]). This risk decreased quite rapidly with time so that the relative risks of being admitted to hospital with venous thromboembolism in the first

and second weeks following an international flight were 3.84 and 1.94 respectively. All of the flight-related cases in the present study developed symptoms of venous thromboembolism within eight days of a journey of more than eight hours' duration. Sensitivity analyses, which explored the potential impact of the omission of 10 eligible cases and the misclassification of BMI, suggested that the true risk of fatal pulmonary embolism in recent air travellers might have been marginally lower than estimated.

There is evidence to suggest that flight-related venous thromobembolism is more likely to occur in passengers with other risk factors such as thrombophilic mutations (Martinelli et al. 2003; Cannegieter et al. 2006), a history of venous thromboembolism (Paganin et al. 2003) or cardiac disease (Paganin et al. 2003), varicose veins (Paganin et al. 2003), obesity (Paganin et al. 2003; Cannegieter et al. 2006), being very short or very tall (Cannegieter et al. 2006), a history of recent injury (Paganin et al. 2003), and the use of oral contraceptives (Martinelli et al. 2003; Cannegieter et al. 2006).

In the present research it was initially planned, and ethical approval was obtained, to determine whether the cases on whom necropsies had been performed had the factor V Leiden mutation and other prothrombotic mutations by obtaining pathological specimens (small paraffin-imbedded tissue blocks or slides) from the pathologist responsible for the necropsy. This work, which was to have been undertaken in the laboratory of Professor Robin Olds in the Department of Pathology at the University of Otago, proved to be feasible at a practical level but was abandoned for funding reasons. Similarly it would have been feasible to send buccal smears kits to the controls so that their thrombophilia status could also be determined. We were unable to examine the relative risk of fatal pulmonary embolism associated with air travel in other sub-groups, such as oral contraceptive users, since the number of cases was inevitably restricted by the size of the New Zealand population.

11.3 SUMMARY AND IMPLICATONS

These are presented in the next chapter.

PART IV CONCLUSION

CHAPTER 12 SUMMARY AND IMPLICATIONS

12.1 SUMMARY

The research presented in this thesis explored the associations between fatal pulmonary embolism and three particular exposures: oral contraceptives, psychotropic drugs, and long-distance air travel. Mortality rates in users of oral contraceptives and in long-distance air travellers were also estimated. These risks were examined in three inter-related national population-based studies: a case-control study of the use of oral contraceptives and psychotropic drugs, a descriptive study of long-distance air travel, and a case-control study of long-distance air travel. The underlying study population for this research included all men and women aged 15 – 59 years, who died in New Zealand between 1990 and 2000, for whom the underlying cause of death was pulmonary embolism.

12.1.1 Oral contraceptives and fatal pulmonary embolism

The present research was the first to have examined the association between oral contraceptives and fatal pulmonary embolism in a population in which preparations containing the progestogens desogestrel and gestodene were widely used. Compared with non-users, in several analyses women prescribed oral contraceptives in the three months before the index date had a 10-fold increased risk of fatal pulmonary embolism. In an analysis which excluded women who were post-menopausal or had a history of venous thromboembolism, as well as those who were immobilised or pregnant in the two months before the index date, the adjusted odds ratio was 13.1 (95% CI 4.4 – 39.0). In accordance with previous studies of non-fatal events, formulations containing desogestrel and gestodene carried a higher risk than levonorgestrel products; the adjusted odds ratios were 18.8 (95% CI 4.9 – 71.3) and 5.9 (95% CI 1.4 – 25.6) respectively. Moreover, pills containing cyproterone acetate were associated with a higher risk again; the adjusted odds ratio was 20.1 (95% CI 4.4 – 91.4). The absolute risk of death from idiopathic pulmonary embolism in oral contraceptive users was estimated to be 10.5 (95% CI 6.2 – 16.6) per million woman-years.

12.1.2 Psychotropic drugs and fatal pulmonary embolism

Earlier studies had found associations between current use of conventional antipsychotics and non-fatal venous thromboembolism and current use of an atypical agent (clozapine) and fatal events. The present research, however, was the first to have estimated the relative risk of fatal pulmonary embolism in current users of conventional antipsychotics. Taking non-users as the reference category, people prescribed antipsychotic drugs in the three months before the index date had a 13-fold increased risk of fatal pulmonary embolism (adjusted odds ratio 13.3 [95% CI 2.3 – 76.3]). Low-potency antipsychotics carried a 20-fold increase in risk (adjusted odds ratio 20.8 [95% CI 1.7 – 259.0]), with thioridazine being the main drug involved. Antidepressant use was also associated with a significantly increased risk (adjusted odds ratio 4.9 [95% CI 1.1 – 22.5]).

12.1.3 Long-distance air travel and fatal pulmonary embolism

Previous studies which examined the association between air travel and venous thromboembolism were all confined to non-fatal events. Hence, this was the first study to estimate the relative risk of dying from pulmonary embolism following a long-distance flight and the estimates were of the same order of magnitude as previously reported for non-fatal venous thromboembolism. People who had undertaken a flight of more than eight hours' duration were eight times more likely to suffer a fatal pulmonary embolic event than non-travellers; the adjusted odds ratio was 7.9 (95% CI 1.1 – 55.1). The odds ratio for a flight of at least three hours' duration was 1.8 (95% CI 0.5 – 7.1). These results were consistent with the findings of the descriptive study of long-distance air travel in which, allowing for a "healthy traveller effect", the sex and age-adjusted mortality rate from pulmonary embolism was about six times higher for overseas visitors to New Zealand (most of whom would recently have undertaken long-distance flights) than the rate in the resident population of New Zealand (very few of whom would recently have flown long-distance).

In absolute terms, the risk of dying from pulmonary embolism after a long-distance flight appears to be very low. The absolute risks in people aged 15 – 59 years following a flight of at least three hours' duration were 0.5 (95% CI 0.2 – 1.2) and 0.6 (95% CI 0.2 – 1.4) per million arrivals for overseas visitors and New Zealand residents respectively.

The risk in New Zealand residents following a flight of more than eight hours was 1.3 (95% CI 0.4 – 3.0) per million arrivals.

12.1.4 Other risk factors and fatal pulmonary embolism

In the case-control studies, a previous history of venous thromboembolism, superficial venous thrombosis, obesity, a chronic musculoskeletal condition of the lower limbs, prolonged immobility, a hospital admission owing to a medical condition, hormone replacement therapy, and an intellectual disability were associated with an increased risk of fatal pulmonary embolism.

12.2 IMPLICATIONS

12.2.1 The methods

There were both advantages and challenges to undertaking the present population-based research in New Zealand. Some of these factors, which will be discussed below, have implications for the conduct of any epidemiological research in this country, while others are more related to the specific associations which were investigated.

The main challenge to undertaking epidemiological research in New Zealand is the size of the population — at the end of the study period there were just under four million people living in the country. This inevitably requires a careful consideration of the outcomes and exposures which can feasibly be studied here and of the appropriate study design for the research question. With regards to venous thromboembolism and oral contraceptives containing desogestrel and gestodene, New Zealand had the highest proportionate use of these preparations in the world and, as such, this provided both an opportunity and a responsibility to undertake the research described in Part II of this thesis. Nevertheless, the small sample size meant that there was limited power for comparing the risks associated with different oral contraceptive formulations.

New Zealand is an island nation which is relatively geographically isolated. This had two main advantages with regards to the research described in this thesis. First, the population was well-defined, which is a fundamental requirement for undertaking any population-based study. Second, the relative remoteness and the fact that almost all

people arriving in New Zealand do so by air provided a unique opportunity to explore the potential association between long-distance air travel and fatal pulmonary embolism. Moreover, all persons entering and leaving the country are required to complete reasonably detailed arrival and departure cards, and thus reliable denominator data were available for the estimation of absolute risks of fatal pulmonary embolism in long-distance air travellers. In relation to future population-based studies, the well-defined nature of the New Zealand resident population is unlikely to change — indeed, recent international security concerns have ensured that strict immigration checks and border controls will probably continue.

The topography of New Zealand also presented some challenges. Because the population is scattered over two main islands, the hospitals, general practices, and family planning clinics which the cases attended were also widely dispersed. This, combined with poor air and road links to some areas, inevitably meant that a lot of time (and money) was spent travelling to undertake the research. For example, a full day of combined air and car travel was required to reach the general practices of several cases. Incidentally, the visits to these general practices were especially interesting from the perspective of health services provision and, possibly because of their isolation, the general practitioners appeared particularly willing to participate in the research.

In the future, it is possible that advances in information technology and the increasing use of computers to record clinical information will mean that it is not always necessary to physically visit general practices in order to examine records and, for instance, to select controls. A promising precedent in this regard is the safety monitoring undertaken by the New Zealand Pharmacovigilance Centre of a new meningococcal B vaccine, in which an automated system abstracted data from the electronic records of children attending practices that were using MedTech32 practice management software. Indeed, an exciting possibility exists to establish a similar system to the UK GPRD in New Zealand, both to monitor drug safety and to undertake other public health research. Certainly the current population size of New Zealand is very similar to the number of patients enrolled in the UK database.

Nonetheless, there may well be future research projects which still require general practice visits. On such occasions, it would be greatly preferable to enter the relevant

information directly into an electronic questionnaire rather than transcribing it onto paper data abstraction forms, since the latter are not only cumbersome to transport, but they also require a second stage of data entry. The Abbey CATI® software could easily be employed for such a task.

Apart from geographical barriers to obtaining information, there were a number of other factors which either aided or impeded access to the required data. Ethical approval for the research was sought on two occasions — first for the case-control study of the use of oral contraceptives and psychotropic drugs and then for the descriptive and case-control studies of long-distance air travel. When these studies were initiated, it was necessary to obtain ethical approval from 12 regional ethics committees in order to undertake a national study. This was inevitably time consuming and, at times, frustrating — for example, when different committees proposed conflicting conditions for ethical approval. Moreover, it appeared from some of the comments which were received, that the committees in some areas had no members who were familiar with observational epidemiological research. Fortunately, however, this situation has now changed with the advent of a multi-region ethics committee which considers all proposals for national studies. In addition, the National Ethics Advisory Committee, which was established under the New Zealand Public Health and Disability Act 2000, has recently published guidelines for the conduct of observational studies (National Ethics Advisory Committee 2006).

Once ethical approval was obtained, the official mortality data were very promptly provided by the New Zealand Health Information Service. However, because of considerable delays in the provision of information by coroners, the most recent data that could be obtained related to deaths three years earlier. This situation should hopefully be improved with the recent passing of the Coroners Act 2006, under which a new position of Chief Coroner has been established and up to 20 full-time coroners will replace the 55 mostly part-time coroners who were working previously (Coronial Services of New Zealand 2007).

During the 1990s, and subsequently, the New Zealand health system underwent an unprecedented number of structural and philosophical reforms, several of which had an impact on the practicalities of obtaining data. For instance, hospitals moved away from

the traditional model of having medical superintendents and nursing matrons towards a more corporate style of management. Consequently, although all letters which sought permission to view the hospital records of cases were sent to Senior Medical Advisors, and in spite of the fact that all regional ethics committees had given ethical approval for hospital records to be examined, managers at several hospitals required that various committees and legal advisors of their own considered the research (at length) before allowing access to the records. This was particularly noticeable in the larger centres. By contrast, in smaller hospitals in which clinicians were still involved in management, there were fewer delays in granting permission.

There were also changes in primary care which had an impact on the research. For instance, in the 1990s there was a move away from the traditional small-business model of general practice towards other models such as fund-holding practices, union health centres, Maori-led services, nurse and midwife-run family planning clinics, and 24-hour primary care emergency and accident centres. In addition, increasing numbers of doctors left general practice and decreasing numbers of New Zealand-trained doctors entered — as a result, a few of the practices which were visited had been staffed by a succession of overseas-trained long-term locums. Some of these new providers appeared unfamiliar with the system of ethical review and the legitimacy of research based in general practice, and were thus initially uncertain about allowing access to medical records. Furthermore, several general practitioners complained that they felt overwhelmed by increasing amounts of paperwork which was unrelated to patient care. Until they were reassured that they would not be required to abstract any data themselves, these doctors were reluctant to participate in the research. This underlines the importance of continuing to develop research methods, such as automated data abstraction, which do not require any effort on the part of general practitioners.

A more recent development in general practice which has positive implications for future research is the establishment of Primary Health Organisations as part of the Primary Health Care Strategy (Ministry of Health 2007). These organisations are funded to provide primary health care for enrolled populations and their existence will hopefully make it easier to identify the general practitioners of potential cases in future studies. Moreover, it is possible that they might prove to be an efficient means of communicating with general practitioners about proposed research. It is also to be

hoped that the requirement to obtain basic demographic data about enrolled patients will ensure that accurate ethnicity data is recorded in medical records and hence the dismal lack of ethnicity information encountered in this research will not be an issue in the future.

Several problems relating to the storage of medical records were encountered during the course of the research. Some of the larger hospitals sent old files to off-site storage facilities and it proved time-consuming to obtain these records. On the other hand, the storage of records on hospital premises was no guarantee that records would be easily accessible — in several hospitals the filing systems appeared quite disorganised. Also of concern was the fact that while several hospitals kept inpatient records for at least 10 years, they destroyed emergency department records much earlier. It is to be hoped that the increasing use of electronic records in hospitals, especially in emergency departments, will prevent this loss of information in the future.

In general practice, it was surprising to find that some doctors had no idea about how long they were legally required to keep records. Moreover, the approaches to archiving records varied considerably. In some practices, for example, the records of patients who had died or left the practice were filed systematically by name or year of death, whereas in others they were placed in boxes in no particular order or simply tied up with string and then left in ceiling spaces, basements, or even garden sheds. The worst example of this was a practice which had locked the old records in a shed and subsequently lost the key. A locksmith was called to open the shed, whereupon it was found that not only had a hive of bees established itself in the wall, but many records had been partially eaten by rats. It was also worrying that in the instance of the abandoned practice there was no health service or agency which was prepared to take responsibility for storing the records. While developments in information technology may mean that such issues are less likely to be encountered in future studies, the problems met in the present research (the deletion of some electronic files, outdated customised computer software, and the use of now defunct 5½ inch floppy disks) should also sound a note of caution about the need for considerable thought regarding the most appropriate way to save electronic records. Moreover, in the absence of any appropriate repository external to individual general practices, it is conceivable that archived electronic records could be

lost even more easily than paper files when practices upgrade their computer systems or a practice closes down.

The descriptive and case-control studies of long-distance air travel, and other case-control studies previously undertaken in the Department of Preventive and Social Medicine, show that it is possible to attain very high response rates when such investigations are undertaken in New Zealand. Of particular note in the current work, was the positive response of the next of kin. Several people explicitly stated at the outset that they were pleased the research was being undertaken and most next of kin wished to receive a summary of the results. At the conclusion of the study, several relatives also wrote to thank us for carrying out the investigation. Given that some of the regional committees which gave approval for the present research were initially very concerned about the proposal to interview next of kin, it might be helpful to describe this positive experience when applying for ethical approval of any future study which requires contact with relatives.

A high response rate was also achieved among potential controls, with only about 7% directly declining to take part in the study. Moreover, 92% of those included in the final analyses wanted to be sent a summary of the findings.

Unfortunately, there are several potential threats to achieving such high participation rates in future studies. First, there is no population register which includes all children and adults living in New Zealand. The most complete source of information about the population aged 18 years and over is the electoral roll. However, because the New Zealand population is increasingly mobile, any copies of the roll which are obtained from the Electoral Enrolment Centre rapidly become out of date. For example, before sending out a summary of the research findings (Appendix A, letters 26 and 27), the contact details of study participants were updated using a recent version of the roll. Nonetheless, a surprising number of letters were returned because people had already shifted from their listed addresses. Given that there is a considerable fee attached to obtaining electronic copies of the electoral roll, it is not practicable to receive regular updates. Second, the low response rate to the letters which were sent during the present research highlights the importance of being able to contact potential study participants by telephone. However, with the burgeoning use of mobile telephones with unlisted

numbers, this is likely to become more difficult in the future. Third, the increasing trend towards telemarketing also poses a threat — indeed, one or two of the people who declined to take part in the research expressed annoyance at being bothered by unsolicited telephone calls. In this context, it will be even more important than ever to send letters to potential participants before attempting to telephone them. Fourth, in the present research, considerable use was made of the Births, Deaths, and Marriages Registry records — for example, to identify additional next of kin of cases and to establish whether people who could not be traced had died or changed their names. There is currently a bill before a Parliamentary Select Committee, the Births, Deaths, Marriages, and Relationships Registration Amendment Bill, which, among other changes, proposes to restrict public access to registered information about other individuals. At present, the proposed amendments would allow access to such records for health research provided that the Registrar-General is "satisfied that benefit to the public of allowing the information to be obtained outweighs the effect on individual privacy" (Births, Deaths, Marriages, and Relationships Registration Amendment Bill 2006). If the amendment is passed, it is to be hoped that this statement will be interpreted in such a way as to permit continued access to information for epidemiological studies which have ethical approval.

12.2.2 The results

Oral contraceptives and venous thromboembolism

The voluntary system for reporting adverse drug reactions in New Zealand fulfilled its primary role by providing an early warning of an excess number of deaths from pulmonary embolism among women taking oral contraceptives containing desogestrel and gestodene. However, the finding that only about a third of the total number of pulmonary embolism deaths among oral contraceptive users were reported to the Centre for Adverse Reactions Monitoring highlights the major limitation of such spontaneous reporting systems and reinforces the need to follow up so-called "safety signals" with systematic ascertainment of adverse reactions in users of medicines.

Following the publication of the analysis of oral contraceptive use and fatal pulmonary embolism (Parkin et al. 2000), the Ministry of Health held a press conference to publicise the findings and to reiterate the prescribing advice it had issued in July 1996

about the use of oral contraceptives containing desogestrel and gestodene. The Ministry also sent this information to doctors, midwives, and pharmacists along with copies of up-dated patient information leaflets which included a toll-free telephone number that women could ring for further information (Medsafe 2000). The letter to the health professionals also criticised two publications mentioned in Chapter 4 for being "misleading and inaccurate" — these included an article by the spokeswoman for the Family Planning Association and a colleague (Egermayer and Roke 2000), reprints of which had been widely distributed to New Zealand doctors by a pharmaceutical company, and the letter from the New Zealand branch of the Australian and New Zealand College of Obstetricians and Gynaecologists to the New Zealand Medical Journal (New Zealand Committee RANZCOG 2000).

Specific recommendations about oral contraceptives containing cyproterone acetate were made by the Ministry of Health after the publication of the Boston group's study based on the UK GPRD (Vasilakis-Scaramozza and Jick 2001). Prescribers were informed that these pills carried a similar, if not higher, risk of venous thromboembolism than formulations containing desogestrel and gestodene and were reminded that cyproterone acetate preparations were only indicated for use in New Zealand by women with androgen-dependent conditions and polycystic ovary syndrome, and for oral contraception in such women (Medsafe 2002). This advice was important, because although the market share of these pills was not high, it was increasing. Indeed, at that time cyproterone acetate preparations were being heavily promoted, almost as cosmetics, in magazines read primarily by young women.

Psychotropic drugs and venous thromboembolism

In 2001, restrictions were placed on the prescription of thioridiazine, the antipsychotic which was primarily implicated in the present research (Medsafe 2001b). Because of concerns about the increased risk of fatal arrhythmias, the initiation of thioridazine therapy was restricted to psychiatrists and the drug was to be used as third-line therapy only. Later, in July 2005, supplies of thioridazine were discontinued by one of the two pharmaceutical companies which supplied the drug in New Zealand (Medsafe 2005).

With regards to the excess risk of venous thromboembolism in current users of other antipsychotics, this should be weighed against the benefits these drugs confer in people

with psychotic disorders. For example, total mortality from all causes has been shown to be lower in schizophrenics who are current users of clozapine than in former users, mostly due to a striking reduction in deaths from suicide (Walker et al. 1997). In patients aged 10 – 54 years, the standardised mortality rate for suicide among past users of clozapine was 222 per 100,000 person-years, whereas the rate of fatal pulmonary embolism in current users was only 30 per 100,000 person-years. Thus, for most people with psychotic illnesses (even those with major risk factors for venous thromboembolism) it is clearly inappropriate to place restrictions on the prescription of antipsychotic medicines in the hope of preventing venous thromboembolism. Instead, attention should be focussed on other primary and secondary preventive measures such as minimising immobilisation and avoiding delays in the diagnosis of venous thromboembolism. Because physical illness often goes unrecognised in people with psychiatric disorders (Licht et al. 1993; Hewer et al. 1995), it is important that prescribers and carers of people taking antipsychotics are especially vigilant with regards to possible signs and symptoms of venous thromboembolism. It is also vital that sudden deaths in users of antipsychotics are thoroughly investigated.

One final comment can be made about the use of antipsychotic drugs — it would seem prudent to avoid prescribing antipsychotic medicines in situations in which they are not strictly indicated. One of the cases in the present research, for example, had been prescribed an antipsychotic drug for the treatment of simple insomnia.

An association between antidepressant drugs and venous thromboembolism has not been described previously. If the association between these medicines and fatal pulmonary embolism is real, it needs to be established whether the drugs increase the risk of venous thromboembolism, or whether people with depression who develop the condition are simply more likely to die. Antidepressants are widely used, and further studies are required to clarify the association between these drugs and venous thromboembolism. To this end, I have initiated a record-linkage study, based on prescription and hospital discharge data, to further investigate the potential association. This method of studying medicine safety has not been explored in New Zealand and if the approach proves feasible, this will allow the investigation of potential adverse reactions to medicines in a more timely manner than has been possible to date.

Long-distance air travel and venous thromboembolism

While this study confirmed that long-distance air travellers have a greater risk of dying from pulmonary embolism than non-travellers, it was reassuring to find that fatal events were rare in relatively healthy persons aged 15 – 59 years. Risks of the order of one in a million are much lower than recent publicity about the "economy class syndrome" has implied.

Other risk factors and venous thromboembolism

Finally, the observed association between intellectual disability and fatal pulmonary embolism warrants further investigation. It may be that people with such disabilities do indeed have a greater risk of venous thromboembolism, or conversely that such events are more likely to prove fatal because of delays in diagnosis and the initiation of treatment. The latter situation would imply a need for greater vigilance on the part of caregivers.

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January 2008

Risk Factors for Venous Thromboembolism

Lianne Parkin

A thesis submitted for the degree of
Doctor of Philosophy
at the University of Otago, Dunedin,
New Zealand.

August 2007

TABLE OF CONTENTS

VOLUME 2

APPENDICES

APPENDIX A: LETTERS

Case-control study of the use of oral contraceptives and psychotropic drugs
(letters 1 – 18)

Descriptive and case-control studies of long-distance air travel
(letters 19 – 25)

Letter 1: Sent to pathologists to request copies of Police 47 forms for women aged 15 – 49 years who died from pulmonary embolism between January 1990 and August 1998

Dear Dr_____

We have been contracted by the Ministry of Health to carry out a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

We are interested in documenting the clinical course of the fatal episode for each woman, including any symptoms of venous thromboembolism that she may have reported in the days and hours before death. In many cases we have found the narrative section of the Police 47 form to be a valuable source of this information. In order to carry out the study, we also need to contact the usual general practitioner of each woman.

We understand that an autopsy was performed at the request of the Coroner in *(name of mortuary)* on the woman named on the enclosed sheet. You will see that we have indicated on the sheet what information we are seeking about this patient. We would be extremely grateful if you were able to send us this information in the enclosed reply-paid envelope.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealand women.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 2: Sent to pathologists to request copies of Police 47 forms for women aged 50 – 59 years and men aged 15 – 59 years who died from pulmonary embolism between January 1990 and December 1998, as well as women aged 15 – 49 years who died between September and December 1998

Dear Dr_____

Recently we conducted a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. A copy of our report is enclosed. This study has now been expanded to include men and women up to the age of 59 years. The aim of the study, which is supported by the Ministry of Health, is to identify risk factors and possible means of preventing such deaths in the future.

We are interested in documenting the clinical course of the fatal episode for each patient, including any symptoms of venous thromboembolism that he or she may have reported in the days and hours before death. In many cases we have found the narrative section of the Police 47 form to be a valuable source of this information. In order to carry out the study, we also need to contact the usual general practitioner of each patient.

We understand that a necropsy was performed at the request of the Coroner in the *(name of mortuary)* on the *(man / woman)* named on the enclosed sheet. You will see that we have indicated on the sheet what information we are seeking about this patient. We would be extremely grateful if you were able to send us this information in the enclosed reply-paid envelope.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealanders.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 3: Sent to pathologists to request copies of Police 47 forms for men and women aged 15 – 59 years who died from pulmonary embolism between January 1999 and December 2000

Dear Dr_____

Recently we conducted a confidential study of deaths from pulmonary embolism in New Zealand men and women aged 15 – 59 years, who died between 1990 and 1998. A copy of our report is enclosed. We have now expanded this study to include people who died in 1999 and 2000. The aim of the study, which is supported by the Ministry of Health, is to identify risk factors and possible means of preventing such deaths in the future.

We are interested in documenting the clinical course of the fatal episode for each patient, including any symptoms of venous thromboembolism that he or she may have reported in the days and hours before death. In many cases we have found the narrative section of the Police 47 form to be a valuable source of such information. In order to carry out the study, we also need to contact the usual general practitioner of each patient.

We understand that a necropsy was performed at the request of the Coroner in the *(name of mortuary)* on the *(man / woman)* named on the enclosed sheet. You will see that we have indicated on the sheet what information we are seeking about this patient. We would be extremely grateful if you were able to send us this information in the enclosed reply-paid envelope.

This study has received approval from all regional Ethics Committees, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealanders.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 4: Sent to a coroner to request a copy of a Police 47 form

Dear_____

As discussed with you today, we have been contracted by the Ministry of Health to carry out a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

We are interested in documenting the clinical course of the fatal episode for each woman, including any symptoms of venous thromboembolism that she may have reported in the days and hours before death. In many cases we have found the narrative section of the Police 47 form to be a valuable source of this information.

As I mentioned, we would be extremely grateful if you were able to send us a copy of the Police 47 form for *(name of woman)*.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealand women.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 5: Sent to senior medical advisors about women aged 15 – 49 years who died from pulmonary embolism in hospital between January 1990 and August 1998

Dear Dr_____

We have been contracted by the Ministry of Health to carry out a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

We understand that the patient listed on the enclosed sheet died from pulmonary embolism in *(name of hospital)* on *(date)*. We would be extremely grateful for your help in obtaining the information we require. Initially we are seeking a copy of the front sheet from the medical records of this patient. We would also like to arrange for one of us (Dr Lianne Parkin) to visit your Hospital and examine the complete records at a later date.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealand women. **Please could you initially send us a photocopy of the front sheet of this patient's case notes?** We will then contact you by telephone to ask about a suitable date for a visit, and to provide any other information you would like.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 6: Sent to senior medical advisors about women aged 15 – 49 years who died from pulmonary embolism between January 1990 and August 1998, and who were admitted to hospital in the year before their death

Dear Dr_____

We have been contracted by the Ministry of Health to carry out a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

We understand that the patient listed on the enclosed sheet was admitted to *(name of hospital)* in the year prior to her death from pulmonary embolism on *(date)*. We would be extremely grateful for your help in obtaining the information we require. Initially we are seeking a copy of the front sheet of the medical records that relates to the last admission of this patient. We would also like to arrange for one of us (Dr Lianne Parkin) to visit your Hospital and examine the complete records at a later date.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealand women. **Please could you initially send us a photocopy of the front sheet of this patient's case notes?** We will then contact you by telephone to ask about a suitable date for a visit, and to provide any other information you would like.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 7: Sent to senior medical advisors about women aged 50 – 59 years and men aged 15 – 59 years who died from pulmonary embolism in hospital between January 1990 and December 1998, as well as women aged 15 – 49 years who died in hospital between September and December 1998

Dear Dr_____

Recently we conducted a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. A copy of our report is enclosed. This study has now been expanded to include men and women up to the age of 59 years. The aim of the study, which is supported by the Ministry of Health, is to identify risk factors and possible means of preventing such deaths in the future.

We understand that the patient listed on the enclosed sheet died from pulmonary embolism in *(name of hospital)* on *(date)*. We would be extremely grateful for your help in obtaining the information we require. Initially we are seeking a copy of the front sheet from the medical records of this patient. This is so that we can identify the patient's general practitioner. We would also like to arrange for one of us (Dr Lianne Parkin) to visit your Hospital and examine the complete records at a later date.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealanders. **Please could you initially send us a photocopy of the front sheet of this patient's case notes in the enclosed reply-paid envelope?** We will then contact you by telephone to ask about a suitable date for a visit, and to provide any other information you would like.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 8: Sent to senior medical advisors about women aged 50 – 59 years and men aged 15 – 59 years who died from pulmonary embolism between January 1990 and December 1998, as well as women aged 15 – 49 years who died between September and December 1998, and who were admitted to hospital in the year before their death

Dear Dr_____

Recently we conducted a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. A copy of our report is enclosed. This study has now been expanded to include men and women up to the age of 59 years. The aim of the study, which is supported by the Ministry of Health, is to identify risk factors and possible means of preventing such deaths in the future.

We understand that the patient listed on the enclosed sheet was admitted to *(name of hospital)* in the year before *(his / her)* death from pulmonary embolism on *(date)*. We would be extremely grateful for your help in obtaining the information we require. Initially we are seeking a copy of the front sheet of the medical records that relates to the last admission of this patient. This is so that we can identify the patient's general practitioner. We would also like to arrange for one of us (Dr Lianne Parkin) to visit your Hospital and examine the complete records at a later date.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealanders. **Please could you initially send us a photocopy of the front sheet of this patient's case notes in the enclosed reply-paid envelope?** We will then contact you by telephone to ask about a suitable date for a visit, and to provide any other information you would like.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 9: Sent to senior medical advisors about men and women aged 15 – 59 years who died from pulmonary embolism in hospital between January 1999 and December 2000

Dear Dr_____

You may remember that recently we conducted a confidential study of deaths from pulmonary embolism in New Zealand men and women aged 15 – 59 years, who died between 1990 and 1998. A copy of our report is enclosed. We have now expanded this study to include people who died in 1999 and 2000. The aim of the study, which is supported by the Ministry of Health, is to identify risk factors and possible means of preventing such deaths in the future.

We understand that the patient listed on the enclosed sheet died from pulmonary embolism in *(name of hospital)* on *(date)*. We would be extremely grateful for your help in obtaining the information we require. Initially we are seeking a copy of the front sheet from the medical records of this patient. This is so that we can identify the patient's general practitioner. We would also like to arrange for one of us (Dr Lianne Parkin) to visit your hospital and examine the complete records at a later date.

This study has received approval from all regional Ethics Committees, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealanders. **Please could you initially send us a photocopy of the front sheet of this patient's case notes in the enclosed reply-paid envelope?** We will then contact you by telephone to ask about a suitable date for a visit, and to provide any other information you would like.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 10: Sent to senior medical advisors about men and women aged 15 – 59 years who died from pulmonary embolism between January 1999 and December 2000, and who were admitted to hospital in the year before their death

Dear Dr_____

You may remember that recently we conducted a confidential study of deaths from pulmonary embolism in New Zealand men and women aged 15 – 59 years, who died between 1990 and 1998. A copy of our report is enclosed. We have now expanded this study to include people who died in 1999 and 2000. The aim of the study, which is supported by the Ministry of Health, is to identify risk factors and possible means of preventing such deaths in the future.

We understand that the patient listed on the enclosed sheet was admitted to *(name of hospital)* in the year before *(his / her)* death from pulmonary embolism on *(date)*. We would be extremely grateful for your help in obtaining the information we require. Initially we are seeking a copy of the front sheet of the medical records that relate to the last admission of this patient. This is so that we can identify the patient's general practitioner. We would also like to arrange for one of us (Dr Lianne Parkin) to visit your hospital and examine the complete records at a later date.

This study has received approval from all regional Ethics Committees, and meets the requirements of the Health Information Privacy Code. We will be taking particular care to safeguard confidentiality.

We would greatly appreciate your help in this study, which could be important for the health of New Zealanders. **Please could you initially send us a photocopy of the front sheet of this patient's case notes in the enclosed reply-paid envelope?** We will then contact you by telephone to ask about a suitable date for a visit, and to provide any other information you would like.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 11 Sent to locums to enquire about the names of the general practitioners of women aged 15 – 49 years who died from pulmonary embolism between January 1990 and August 1998

Dear Dr_____

We have been contracted by the Ministry of Health to carry out a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

We understand that on *(date)* whilst working in / for *(name of town / name of general practice)*, you attended the patient listed on the enclosed sheet who died from pulmonary embolism at *(place of death)*. In order to carry out the study, we need to contact the usual general practitioner of this woman. We would be very grateful if you were able to write the name and address of this doctor on the attached sheet, and return this in the reply-paid envelope.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. We have a professional obligation of confidentiality as medical practitioners ourselves, and we give an undertaking that no information about any named patient or doctor will be provided to any other party.

We would greatly appreciate your help in this study, which could be important for the health of New Zealand women.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 12 Sent to locums to enquire about the names of the general practitioners of women aged 50 – 59 years and men aged 15 – 59 years who died from pulmonary embolism between January 1990 and December 1998, and of women aged 15 – 49 years who died between September and December 1998

Dear Dr_____

Recently we conducted a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. A copy of our report is enclosed. This study has now been expanded to include men and women up to the age of 59 years. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

We understand that on *(date)* whilst working in / for *(name of town / name of general practice)*, you attended the patient listed on the enclosed sheet who died from pulmonary embolism at *(place of death)*. In order to carry out the study, we need to contact the usual general practitioner of this patient. We would be very grateful if you were able to write the name and address of this doctor on the attached sheet, and return this in the reply-paid envelope.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. We have a professional obligation of confidentiality as medical practitioners ourselves, and we give an undertaking that no information about any named patient or doctor will be provided to any other party.

We would greatly appreciate your help in this study, which could be important for the health of New Zealanders.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 13 Sent to next of kin to enquire about name of their relative's general practitioner

Dear _____

I was very sorry to learn that your *(husband / wife / partner)* died from pulmonary embolism in *(year)*. My colleagues and I have been asked by the Ministry of Health to conduct a study into the causes of this condition. Our aim is to identify factors that could help in preventing such cases in the future.

In order to carry out the study, we need to contact the main general practitioner used by your *(husband / wife / partner)* in recent years. Please would you be kind enough to write the name and address of this doctor on the attached sheet, and return this in the reply-paid envelope? You will see that we are also asking whether you would like to receive information about the findings of our survey when it is completed.

Thank you very much indeed for your help. If you would like to discuss any aspects of this study, please don't hesitate to call me collect on (03) 479 7205.

Yours sincerely

David Skegg
Professor of Preventive and Social Medicine

Letter 14 Thank you letter sent to the next of kin who provided the name of their relative's general practitioner

Dear _____

Thank you very much for returning our form detailing the name and address of your *(wife's / husband's / partner's)* general practitioner. Your help is most appreciated.

We will send you information about the findings of the pulmonary embolism study when it is completed.

With many thanks once again,

Yours sincerely

David Skegg
Professor of Preventive and Social Medicine

Letter 15 Sent to general practitioners about women aged 15 – 49 years who died from pulmonary embolism between January 1990 and August 1998

Dear Dr_____

We have been contracted by the Ministry of Health to carry out a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

We understand that the patient listed on the enclosed sheet was a member of your practice. We would be extremely grateful for your help in obtaining the required information. This would involve a brief visit from one of us (Dr Lianne Parkin), to examine the medical records of this patient and of four randomly selected controls. Although it would be valuable if you could help to interpret the notes, we believe that this visit should cause you minimal inconvenience.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. None of the information recorded will be linked with the names of individual patients or of the particular practice. We have a professional obligation of confidentiality as medical practitioners ourselves, and we give an undertaking that no information about any named patient or doctor will be provided to any other party.

We would greatly appreciate your help in this study, which could be important for the health of New Zealand women. One of us will contact you by telephone to ask about a suitable date for a visit, and to provide any other information you would like.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 16 Sent to general practitioners about women aged 50 – 59 years and men aged 15 – 59 years who died from pulmonary embolism between January 1990 and December 1998, as well as women aged 15 – 49 years who died between September and December 1998

Dear Dr_____

Recently we conducted a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. A copy of our report is enclosed. This study has now been expanded to include men and women up to the age of 59 years. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

We understand that the patient listed on the enclosed sheet was a member of your practice. We would be extremely grateful for your help in obtaining the required information. This would involve a brief visit from one of us (Dr Lianne Parkin) to examine the medical records of this patient and of four randomly selected controls. Although it would be valuable if you could help to interpret the notes, we believe that this visit should cause you minimal inconvenience.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. None of the information recorded will be linked with the names of individual patients or of the particular practice. We have a professional obligation of confidentiality as medical practitioners ourselves, and we give an undertaking that no information about any named patient or doctor will be provided to any other party.

We would greatly appreciate your help in this study, which could be important for the health of New Zealanders. One of us will contact you by telephone to ask about a suitable date for a visit, and to provide any other information you would like.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 17 Sent to general practitioners about men and women aged 15 – 59 years who died from pulmonary embolism between January 1999 and December 2000

Dear Dr_____

Recently we conducted a confidential study of deaths from pulmonary embolism in New Zealand men and women aged 15 – 59 years, who died between 1990 and 1998. A copy of our report is enclosed, along with a report from an earlier study in women of child-bearing age. We have now expanded the study to include people who died in 1999 and 2000. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

We understand that the patient listed on the enclosed sheet was a member of your practice. We would be extremely grateful for your help in obtaining the required information. This would involve a brief visit from one of us (Dr Lianne Parkin) to examine the medical records of this patient. Although it would be valuable if you could help to interpret the notes, we believe that this visit should cause you minimal inconvenience.

This study has received approval from all regional Ethics Committees, and meets the requirements of the Health Information Privacy Code. None of the information recorded will be linked with the name of the individual patient or of the particular practice. We have a professional obligation of confidentiality as medical practitioners ourselves, and we give an undertaking that no information about any named patient or doctor will be provided to any other party.

We would greatly appreciate your help in this study, which could be important for the health of New Zealanders. One of us will contact you by telephone to ask about a suitable date for a visit, and to provide any other information you would like.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 18 Sent to the New Zealand Family Planning Association about the case-control study of oral contraceptive use and fatal pulmonary embolism

Dear Dr_____

We have been contracted by the Ministry of Health to carry out a confidential study of deaths from pulmonary embolism in New Zealand women of child-bearing age. The aim of the study is to identify risk factors and possible means of preventing such deaths in the future.

As well as a descriptive element, the study has a case-control component in which the use of oral contraceptives will be compared in women who died from pulmonary embolism and an appropriate comparison group.

Although the main source of information for cases and controls will be general practitioner records, we are aware that many women attend Family Planning Clinics to obtain oral contraceptives, and we are therefore writing to seek the assistance of the New Zealand Family Planning Association in obtaining the information we require. This would involve a visit by one of us (Dr Lianne Parkin) to various NZFPA clinics to examine any records that exist for the deceased women and control women.

This study has received ethical approval, and meets the requirements of the Health Information Privacy Code. None of the information recorded will be linked with the names of individual women, particular NZFPA clinics, or staff. We have a professional obligation of confidentiality as medical practitioners ourselves, and we give an undertaking that no information about any named women, NZFPA clinics, or staff will be provided to any other party.

We would greatly appreciate your help in this study, which could be important for the health of New Zealand women. We have enclosed a confidential copy of the study protocol, but please let us know if you would like any further information.

Yours sincerely

Lianne Parkin
Research Fellow

David Skegg
Professor

Letter 19 Sent to next of kin of New Zealand men and women aged 15 – 59 years who died from pulmonary embolism between January 1990 and December 2000 (next of kin who had not previously been contacted), descriptive and case-control studies of long-distance air travel

Dear _____

We were very sorry to learn that your *(husband / wife / partner)* died from pulmonary embolism in *(year)*. The Department of Preventive Medicine at the Otago Medical School is conducting a study into the causes of this condition, with patients being identified from national mortality records. Our aim is to look for factors that could help in preventing deaths in the future. The study has received ethical approval from the Otago Ethics Committee on behalf of all regional ethics committees.

We would be extremely grateful if you would agree to take part in this study. We would like to interview you by telephone about aspects of your *(husband's / wife's / partner's)* life before *(he / she)* developed pulmonary embolism. The interview will take about 20 minutes of your time; the interviewer will be _____. If you agree to take part, all the information you give us will be recorded without names and will be kept strictly confidential. You do not need to answer all the questions, and you may stop the interview at any time.

One of us will contact you by telephone during the next two weeks to request your permission for the interview. In the meantime, we would be most grateful if you could correct your address and telephone number on the attached form if necessary, and mark the most convenient time for us to telephone. Please could you return this form in the reply-paid envelope?

If you would like advice as to your rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate, telephone *(relevant phone number)*.

We do very much hope that you will agree to take part in this study. We believe that the results of the study could be important to the health of New Zealanders.

If you would like to discuss any aspects of this study, please don't hesitate to contact me by mail or by telephoning collect.

Yours sincerely

Dr Lianne Parkin
Ph (03) 479 8425

P.S. A calendar is also enclosed. We will refer to this during the interview.

Please would you complete or correct this form and return it in the reply-paid envelope provided.

Full name _____*(of next of kin)*_____

Address _____*(of next of kin)*_____

_____

_____

Telephone number _____

Mobile number (if you don't have a home phone number) _____

Which days and / or times in the next month would be convenient for us to phone you? (please give as many choices as possible)

Thank you for your help.

Letter 20 Sent to next of kin of New Zealand men and women aged 15 – 59 years who died from pulmonary embolism between January 1990 and December 2000 (next of kin who had previously been contacted), descriptive and case-control studies of long-distance air travel

Dear _____

(Last year / In 1999) we wrote to you about a study we are conducting into the causes of pulmonary embolism and we asked you for the name of your *(husband's / wife's / partner's)* general practitioner. The aim of our study is to identify factors that could help in preventing cases of pulmonary embolism in the future. The study has received ethical approval from the Otago Ethics Committee on behalf of all regional ethics committees.

We would be extremely grateful if you would agree to take part in the final phase of our study. We would like to interview you by telephone about aspects of your *(husband's / wife's / partner's)* life before *(he / she)* developed pulmonary embolism. The interview will take about 20 minutes of your time; the interviewer will be _____. If you agree to take part, all the information you give us will be recorded without names and will be kept strictly confidential. You do not need to answer all the questions, and you may stop the interview at any time.

One of us will contact you by telephone during the next two weeks to request your permission for the interview. In the meantime, we would be most grateful if you could correct your address and telephone number on the attached form if necessary, and mark the most convenient time for us to telephone. Please could you return this form in the reply-paid envelope?

If you would like advice as to your rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate, telephone *(relevant phone number).*

We do very much hope that you will agree to take part in this study. We believe that the results of the study could be important to the health of New Zealanders.

If you would like to discuss any aspects of this study, please don't hesitate to contact one of us by mail or by telephoning collect.

Yours sincerely

Dr Lianne Parkin
Ph (03) 479 8425

Professor David Skegg
Ph (03) 479 7205

P.S. A calendar is also enclosed. We will refer to this during the interview.
Please would you complete or correct this form and return it in the reply-paid envelope provided.

Full name _____*(of next of kin)*_____

Address _____*(of next of kin)*_____

_____

_____

Telephone number _____

Mobile number (if you don't have a home phone number) _____

Which days and / or times in the next month would be convenient for us to phone you? (please give as many choices as possible)

Thank you for your help.

Letter 21: Sent to next of kin of overseas visitors aged 15 – 59 years who died from pulmonary embolism in New Zealand between January 1990 and December 2000 (presumed English speakers), descriptive and case-control studies of long-distance air travel

Dear _____

We were very sorry to learn that your *(husband / wife / partner)* died from pulmonary embolism in New Zealand. The Department of Preventive Medicine at the Otago Medical School in New Zealand is conducting a study into the causes of this condition, with patients being identified from New Zealand mortality records. Our aim is to look for factors that could help in preventing deaths in the future. The study has received ethical approval from all the New Zealand Health and Disability Ethics Committees.

We would be extremely grateful if you would agree to take part in this study. We would like to interview you by telephone about aspects of your *(husband's / wife's / partner's)* life before *(he / she)* developed pulmonary embolism. The interview will take about 20 minutes of your time; the interviewer will be _____. If you agree to take part, all the information you give us will be recorded without names and will be kept strictly confidential. You do not need to answer all the questions, and you may stop the interview at any time.

One of us will contact you by telephone during the next four weeks to request your permission for the interview. In the meantime, we would be most grateful if you could correct your address and telephone number on the attached form if necessary, and mark the most convenient time for us to telephone. Please could you return this form in the enclosed envelope?

We do very much hope that you will agree to take part in this study. If you would like to discuss any aspects of the study, please don't hesitate to contact us by mail or by telephoning collect.

Yours sincerely

Dr Lianne Parkin
Tel 64 3 479 8425

Professor David Skegg

P.S. A calendar is also enclosed. We will refer to this during the interview.

Please would you complete or correct this form and return it in the reply-paid envelope provided.

Full name _____*(of next of kin)*_____

Address _____*(of next of kin)*_____

_____

_____

Telephone number _____

Mobile number (if you don't have a home phone number) _____

Which days and / or times in the next month would be convenient for us to phone you? (please give as many choices as possible)

Thank you for your help.

Letter 22: Sent to next of kin of overseas visitors aged 15 – 59 years who died from pulmonary embolism in New Zealand between January 1990 and December 2000 (possible non-fluent speakers of English), descriptive and case-control studies of long-distance air travel

Dear _____

We were very sorry to learn that your *(husband / wife / partner)* died from pulmonary embolism in New Zealand. The Department of Preventive Medicine at the Otago Medical School in New Zealand is conducting a study into the causes of this condition, with patients being identified from New Zealand mortality records. Our aim is to look for factors that could help in preventing deaths in the future. The study has received ethical approval from all the New Zealand Health and Disability Ethics Committees.

We would be extremely grateful if you would agree to take part in this study. We would like to interview you by telephone about aspects of your *(husband's / wife's / partner's)* life before *(he / she)* developed pulmonary embolism. The interview will take about 20 minutes of your time; the interviewer will be _____. We are happy to provide a medical translator if you would prefer not to be interviewed in English. If you agree to take part, all the information you give us will be recorded without names and will be kept strictly confidential. You do not need to answer all the questions, and you may stop the interview at any time.

One of us will contact you by telephone during the next four weeks to request your permission for the interview. In the meantime, we would be most grateful if you could correct your address and telephone number on the attached form if necessary, and mark the most convenient time for us to telephone. Please could you return this form in the enclosed envelope?

We do very much hope that you will agree to take part in this study. If you would like to discuss any aspects of the study, please don't hesitate to contact us by mail or by telephoning collect.

Yours sincerely

Dr Lianne Parkin
Tel 64 3 479 8425

Professor David Skegg

P.S. A calendar is also enclosed. We will refer to this during the interview.
Please would you complete or correct this form and return it in the reply-paid envelope provided.

Full name _____*(of next of kin)*_____

Address _____*(of next of kin)*_____

_____

_____

_____

Telephone number _____

Preferred language for interview _____

Which days and / or times in the next month would be convenient for us to phone you? (please give as many choices as possible)

Thank you for your help.

Letter 23: Sent to next of kin (of New Zealand residents or overseas visitors) without a traceable telephone number who did not reply to the letter inviting them to take part in the study (descriptive and case-control studies of long-distance air travel and fatal pulmonary embolism)

Dear _____

I hope that you will excuse my writing to you again, but I cannot trace a reply to my previous letter. As my letter (or your reply) may have gone astray in the post, I am enclosing a further copy. If you have replied already, please accept my apologies for putting you to this further trouble, but I am anxious to make this study as complete as possible.

Yours sincerely

Dr Lianne Parkin
Research Fellow

Ph (03) 479 8425

Letter 24: Sent to potential controls, case-control study of long-distance air travel

Dear _____

A major study is being carried out by the Department of Preventive Medicine at the Otago Medical School on the causes of a condition that affects many New Zealanders every year. Our aim is to identify factors that could help in preventing deaths from this condition in the future. The study involves interviewing a large number of men and women all over New Zealand, and has received ethical approval from the Otago Ethics Committee on behalf of all regional ethics committees.

We would very much appreciate your help in this study. Your name was chosen at random from the electoral roll. We would be extremely grateful if you would agree to take part by answering several questions by telephone about aspects of your life and health. The interview will take about 20 minutes of your time; the interviewer will be _____. If you agree to take part, all the information you give us will be recorded without your name and will be kept strictly confidential. You do not need to answer all the questions, and you may stop the interview at any time.

One of us will contact you by telephone during the next two weeks to request your permission for the interview. In the meantime, we would be most grateful if you could correct your address and telephone number on the attached form if necessary, and mark the most convenient time for us to telephone. Please could you return this form in the reply-paid envelope?

If you would like advice as to your rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate, telephone *(relevant phone number).*

We do very much hope that you will agree to take part in this study. We believe that the results of the study could be important to the health of New Zealanders.

If you would like to discuss any aspects of this study, please don't hesitate to contact me by mail or by telephoning collect.

Yours sincerely

Dr Lianne Parkin
Ph (03) 479 8425

P.S. A calendar is also enclosed. We will refer to this during the interview.

Please would you complete or correct this form and return it in the reply-paid envelope provided.

Full name _____

Previous name(s) _____

Address _____

_____

_____

Telephone number _____

Mobile number (if you don't have a home phone number) _____

Date of birth _____

Which days and / or times in the next month would be convenient for us to phone you? (please give as many choices as possible)

Thank you for your help

Letter 25: Sent to potential controls without a traceable telephone number who did not reply to the letter inviting them to take part in the study (case-control study of long-distance air travel and fatal pulmonary embolism)

Dear _____

I hope that you will excuse my writing to you again, but I cannot trace a reply to my previous letter. As my letter (or your reply) may have gone astray in the post, I am enclosing a further copy. If you have replied already, please accept my apologies for putting you to this further trouble, but I am anxious to make this study as complete as possible.

Yours sincerely

Dr Lianne Parkin
Research Fellow

Ph (03) 479 8425

Letter 26: Letter sent to next of kin who participated in the descriptive and case-control studies of long-distance air travel and fatal pulmonary embolism

Dear _____

Thank you very much for helping with our research into risk factors for pulmonary embolism. I apologise for taking so long to write to you, but it took us longer than expected to complete the study.

The final results of the study are to be published this month in an international medical journal, Thrombosis and Haemostasis. I am very happy to send you a copy of this article and two previous ones if you would like to read them, but in the meantime I thought I would send you a summary of the results.

Long-distance air travel

We found that long-distance air travel increased the risk of dying from pulmonary embolism. People who flew more than eight hours had about eight times the risk of dying from pulmonary embolism than non-travellers. However because fatal pulmonary embolism is actually a very rare occurrence, the number of people who developed pulmonary embolism after a flight was very small. For example, we found that for every million people aged between 15 – 59 years who flew for more than eight hours, one passenger died from pulmonary embolism.

Other risk factors

Other factors which increased the risk of dying from pulmonary embolism included previous episodes of deep vein thrombosis (blood clots in the legs) and pulmonary embolism, certain medicines (the combined oral contraceptive pill, hormone replacement therapy, and antipsychotic drugs), obesity, prolonged immobility, and a recent hospital admission.

Once again, I'd like to thank you very much for taking the time to help us with this study. We believe that the results of the study are of importance to the health of New Zealanders. If you would like to receive a copy of the journal articles or discuss any aspects of the study, please don't hesitate to contact me by mail or by telephoning collect.

Yours sincerely

Dr Lianne Parkin
Ph (03) 479 8425

Letter 27: Letter sent to controls who participated in the case-control study of long-distance air travel and fatal pulmonary embolism

Dear _____

Thank you very much for helping with our study of risk factors for pulmonary embolism (blood clots in the lungs). I apologise for taking so long to write to you, but it took us longer than expected to complete the study.

The results of the study are to be published this month in an international medical journal, Thrombosis and Haemostasis. I am very happy to send you a copy of the article if you would like to read it, but in the meantime I thought I would send you a summary of the results.

We found that long-distance air travel increased the risk of dying from pulmonary embolism. People who flew more than eight hours had about eight times the risk of dying from pulmonary embolism than non-travellers. However because fatal pulmonary embolism is actually a very rare occurrence, the number of people who developed pulmonary embolism after a flight was very small. For example, we found that for every million people aged between 15 – 59 years who flew for more than eight hours, one passenger died from pulmonary embolism. This is a much lower risk than media publicity about "economy-class syndrome" has led many people to believe.

Once again, I'd like to thank you very much for taking the time to help us with this study. If you would like to receive a copy of the article, please don't hesitate to contact me.

Yours sincerely

Dr Lianne Parkin
Ph (03) 479 8425

APPENDIX B: DATA ABSTRACTION FORM AND DATA DICTIONARY

Case-control study of the use of oral contraceptives and psychotropic drugs

Data abstraction form

1. Study ID Number:

2. Practice ID Number:

3. Sex:

4. Index date:

5. Date of data abstraction:

6. Date of birth:

7. Date of joining practice:

(If not specifically stated, record date of first clinical consultation)

8. Ethnicity recorded? Yes / No

Details:

9. Were any of the following conditions recorded in the clinical notes <u>before</u> the index date?

(For cases only, if the occurrence of any of these conditions was recorded after the index date, include this information under question 18b.)

(a) Deep vein thrombosis Yes / No ☐

Details, including dates: ☐☐ ☐☐ ☐☐

☐

(b) Superficial venous thrombosis Yes / No ☐

Details, including dates: ☐☐ ☐☐ ☐☐

☐

(c) Varicose veins Yes / No ☐

Details, including dates: ☐☐ ☐☐ ☐☐

☐

(d) Pulmonary embolism Yes / No

Details, including dates:

(e) Hypertension (during pregnancy) Yes / No

Details, including dates:

(f) Hypertension (when not pregnant) Yes / No

Details, including dates:

(g) Myocardial infarction Yes / No

Details, including dates:

(h) Angina Yes / No

Details, including dates:

(i) Stroke Yes / No

Details, including dates:

(j) Transient ischaemic attack Yes / No

Details, including dates:

(k) Other heart or blood vessel disease Yes / No

Details, including dates:

(l) Diabetes mellitus Yes / No

Details, including dates:

(m) Blood disorders

(Factor V Leiden, antithrombin deficiency, protein C or S deficiency, dysfibrinogenaemia, plasminogen deficiency, prothrombin G20210A, high factor VIII, increased platelets, homocysteinaemia, antiphospholipid syndrome / anticardiolipin antibodies / lupus anticoagulant.)

Yes / No ☐

Details, including dates: ☐☐ ☐☐ ☐☐

(n) Cancer

Yes / No ☐

Details, including dates: ☐☐ ☐☐ ☐☐ ☐ ☐ ☐ ☐

(o) Immobility during previous year

Yes / No ☐

Details, including dates: ☐ ☐ ☐

(p) Injuries requiring medical attention during previous year

Yes / No

Details, including dates:

(q) Operations during previous year Yes / No

Details, including dates:

(r) Hysterectomy Yes / No

Details, including dates:

(s) Oophorectomy Yes / No

Details, including dates:

(t) Intellectual disability Yes / No

Details, including dates:

(u) Details of any other significant history:

10. Were any pregnancies recorded in the clinical notes <u>before</u> the index date?

(For cases only, if any information regarding pregnancies was recorded after the index date, include details under question 18b.)

Yes / No ☐

If yes,

(a) Record number of pregnancies:

- Total number of pregnancies: ☐☐
- Miscarriages: ☐☐
- Terminations of pregnancy: ☐☐
- Ectopic pregnancies: ☐☐
- Live births: ☐☐
- Stillbirths: ☐☐

(b) Any pregnancies in the year before the index date? ☐

Yes / No

If yes,

- Estimated date of last menstrual period: ☐☐ ☐☐ ☐☐

- If pregnancy ended before index date,
    - Date pregnancy ended: | | | | | | | | |
    - Approximate gestation (in weeks)when pregnancy ended:

- Was any surgery involved (termination of pregnancy, evacuation of retained products of conception, removal of ectopic pregnancy, other)?

  Yes / No

  Details, including dates:

11. Was smoking status recorded in the clinical notes <u>before</u> the index date?

(For cases only, if any information regarding smoking status was recorded after the index date, include details under question 18b.)

Yes / No | |

If yes,

- Most recently recorded smoking status: (circle) |

  Smoker
  Ex-smoker
  Non-smoker

- Date this was recorded: | | | | | | | | |

- Any other details:

12. Menopausal status.

(For cases only, if any information regarding menopausal status or hormone replacement therapy use was recorded after the index date, include details under question 18b.)

(a) Any record (<u>before</u> the index date) of being post-menopausal?

Yes / No ☐

If yes,

- When was this recorded?
- Date of last period if known: ☐☐ ☐☐ ☐☐

(b) Any record (<u>before</u> the index date) of peri-menopausal symptoms?

Yes / No ☐

If yes,

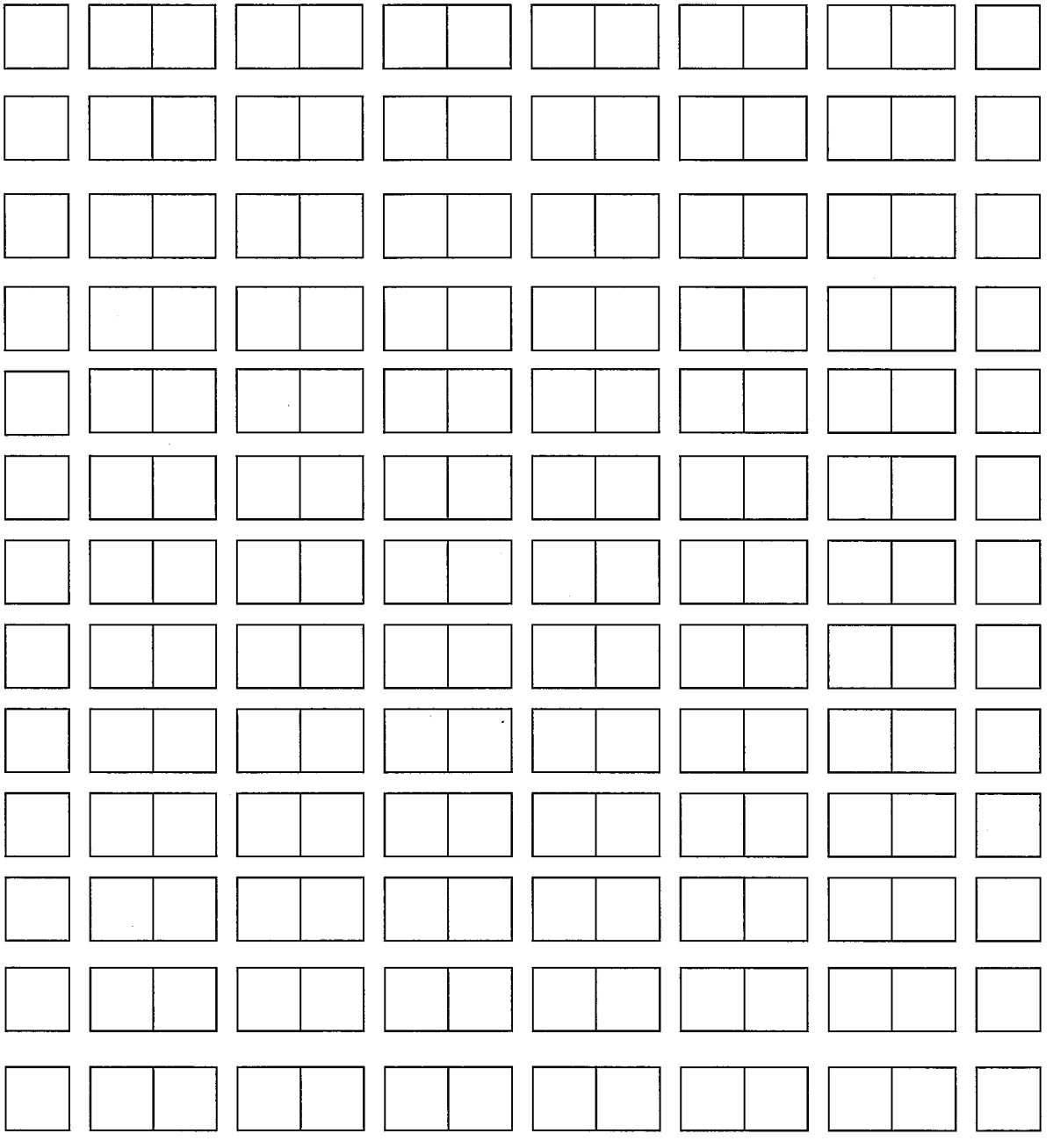
- When was this recorded?
- Duration of symptoms (months), if known:

(c) Any record (<u>before</u> the index date) of hormone replacement therapy use?

Yes / No ☐

If yes,

- Details of all regimens used, including date and duration of each prescription:



13. Was the use of any of the following methods of contraception recorded in the clinical notes <u>before</u> the index date?

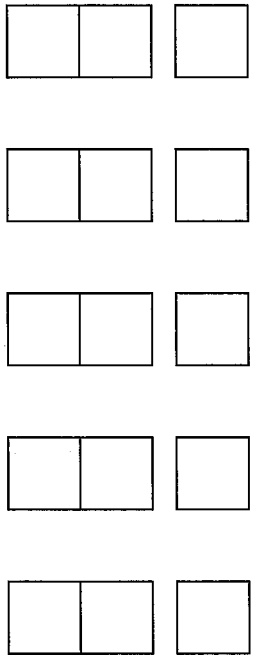
(For cases only, if any information regarding contraceptive history was recorded after the index date, include details under question 18b.)

<u>Index date:</u> __/__/__	**Prior to the year of interest**	**In the year before the index date**		
Oral contraceptives *(including non-contraceptive indications)*	Yes / No	Yes / No	☐	☐
Progestogen-only pill	Yes / No	Yes / No	☐	☐
DMPA ('Depo Provera')	Yes / No	Yes / No	☐	☐
Morning after pill	Yes / No	Yes / No	☐	☐
IUD	Yes / No	Yes / No	☐	☐
Diaphragm	Yes / No	Yes / No	☐	☐
Condoms	Yes / No	Yes / No	☐	☐
Female sterilisation	Yes / No	Yes / No	☐	☐
Partner vasectomy	Yes / No	Yes / No	☐	☐
Natural family planning	Yes / No	Yes / No	☐	☐
Other	Yes/ No	Yes/ No	☐	☐

(Record details of ***<u>all</u> methods used in the year before the index date***, and ***<u>oral contraceptive</u> use prior to the year of interest***, on the following pages.)

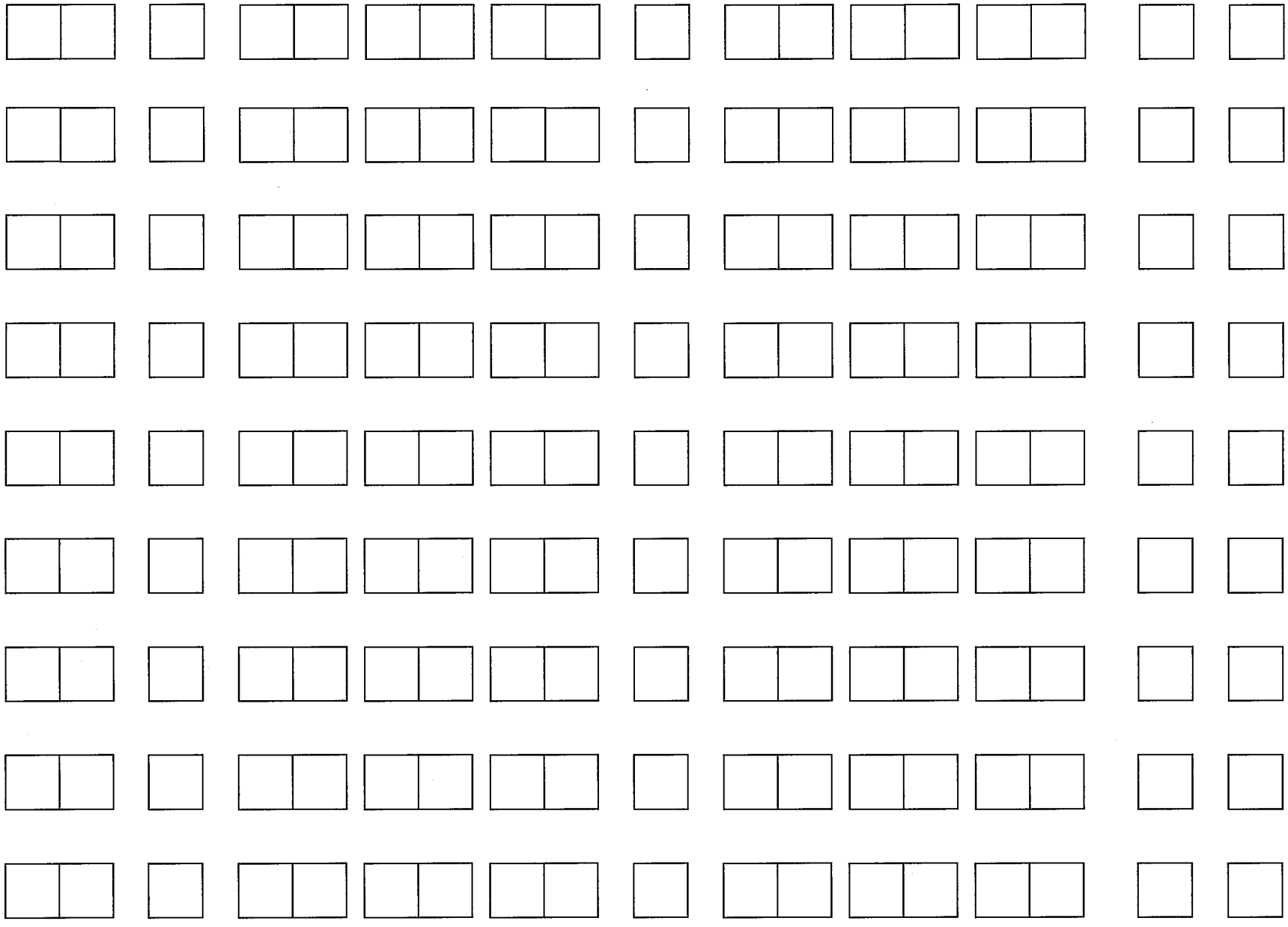
Details of all methods of contraception used in the year before the index date:

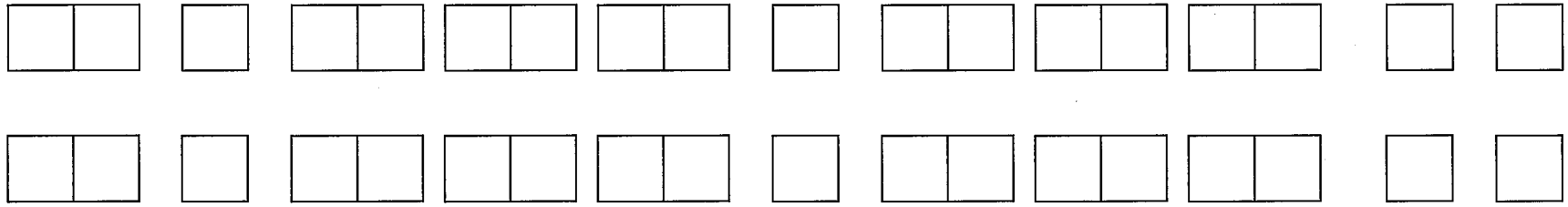
Method	Brand	Date prescribed	Duration of Prescription



Details of any oral contraceptive use prior to the year of interest:

Brand	Date prescribed	Duration of prescription



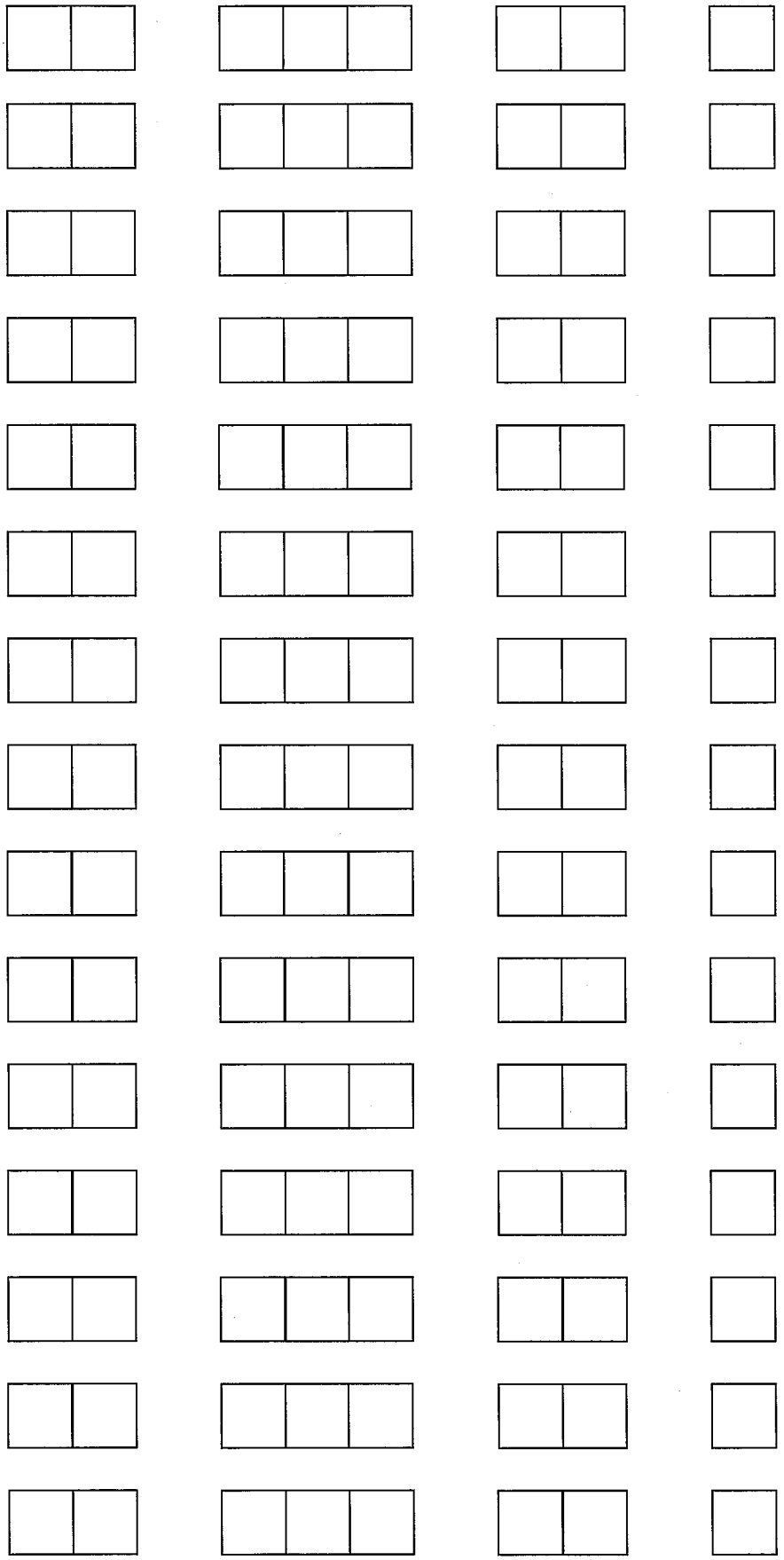


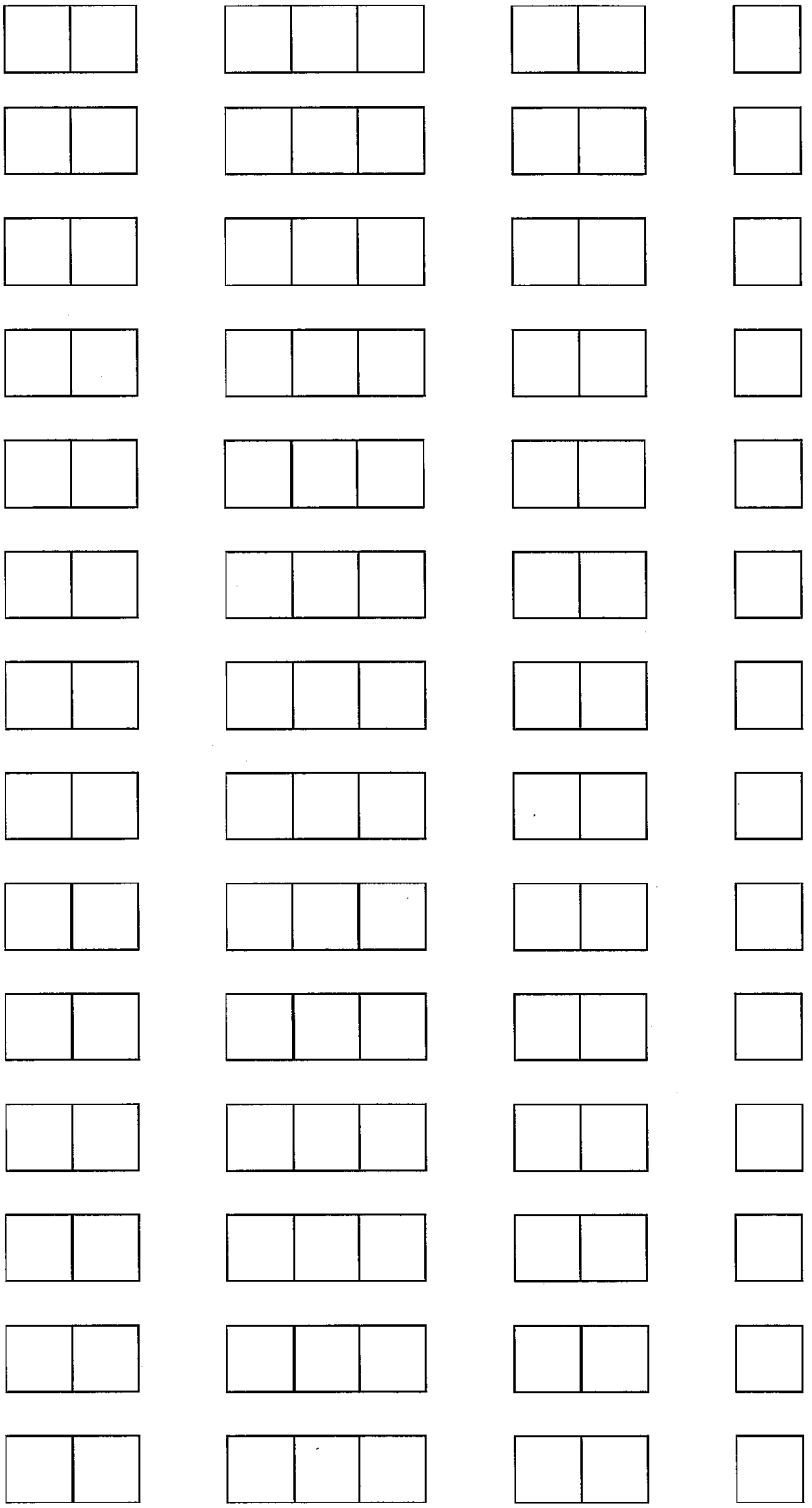
14. Was the use of any other medication recorded in the clinical notes in the year before the index date?

(For cases only, if any information regarding medication use in this year was recorded after the index date, include details under question 18b.)

Yes / No ☐

Details, including dates:





15. Was any information regarding weight recorded in the clinical notes before the index date?

(For cases only, if any information regarding weight was recorded after the index date, include details under question 18b.)

Yes / No ☐

If yes,

- Date weight recorded: ☐☐ ☐☐ ☐☐

☐

- Weight: kilograms __ . _ ☐☐☐ ☐

stone / pounds __/__ ☐☐ ☐☐

- Any narrative comments: ☐

16. Was any information regarding height recorded in the clinical notes before the index date?

(For cases only, if any information regarding height was recorded after the index date, include details under question 18b.)

Yes / No ☐

If yes,

- Date height recorded: ☐☐ ☐☐ ☐☐

- Height: metres __.__ ☐ ☐☐

feet / inches __/__ ☐ ☐☐

- Any narrative comments: ☐

17. Was any family history of venous thromboembolism recorded in the clinical notes before the index date?

(For cases only, if any information regarding a family history of venous thromboembolism was recorded after the index date, include details under question 18b.)

Yes / No ☐

If yes,

- Record details for each affected relative:

(Relationship to woman, deep vein thrombosis / pulmonary embolism, fatal / non-fatal, number of episodes, circumstances, age(s) when venous thromboembolism occurred, known hypercoagulopathies.)

☐

☐

☐

☐

18. For cases;

(a) Details re clinical course and management of fatal episode (if any recorded):

(Note information source e.g. clinical notes, hospital letter, general practitioner recall)

(b) Details of any other relevant history recorded retrospectively (after index date):

Data dictionary

1. Study ID Number: | | | | | | |

2. Practice ID Number: | | | |

3. Case or control? |

1. Case
0. Control

4. Sex: |

1. Female
0. Male

5. Index date: | | | | | |

6. Date of data abstraction: | | | | | |

7. Date of birth: | | | | | |

8. Date of joining practice: | | | | | |

9. Ethnicity recorded?

1. Yes
0. No

10. Ethnicity:

1. European
2. Maori
3. Pacific
4. Asian
5. Other

11. Ethnicity:

(Use this cell if a 2nd ethnic identity was recorded)

12. Recorded diagnosis of deep vein thrombosis (DVT) before index date?

1. Yes
0. No

13. Date 1st episode of DVT diagnosed:

(If unknown, enter date that history of DVT 1st recorded and enter '1' in date indicator box)

14. Date indicator:

(Complete only if date of diagnosis unknown)

15. Number of recorded episodes of DVT: ☐

1. 1
2. 2
3. ≥ 3
4. Not recorded

16. Recorded diagnosis of superficial venous thrombosis (SVT) before index date? ☐

1. Yes
0. No

17. Date 1st episode of SVT diagnosed: ☐☐ ☐☐ ☐☐

(If unknown, enter date that history of SVT 1st recorded and enter '1' in date indicator box)

18. Date indicator: ☐

(Complete only if date of diagnosis unknown)

19. Number of recorded episodes of SVT before index date: ☐

1. 1
2. 2
3. ≥ 3
4. Not recorded

20. Record of varicose veins before index date? ☐

1. Yes
0. No

21. Date presence of varicose veins 1st recorded: ☐☐ ☐☐ ☐☐

22. Recorded history of treatment of varicose veins before index date?

1. Yes
0. No

23. Recorded diagnosis of pulmonary embolism (PE) before index date?

1. Yes
0. No

24. Date 1st episode of PE diagnosed:

(If unknown, enter date that history of PE 1st recorded and enter '1' in date indicator box)

25. Date indicator:

(Complete only if date of diagnosis unknown)

26. Number of recorded episodes of PE before index date:

1. 1
2. 2
3. ≥ 3
4. Not recorded

27. Recorded diagnosis of hypertension during pregnancy before index date?

(Defined as: elevated blood pressure treated by medication and / or hospital admission. Leave blank if male)

1. Yes
0. No

28. Date 1st episode of hypertension during pregnancy diagnosed:

(If unknown, enter date that history of hypertension during pregnancy1st recorded and enter '1' in date indicator box)

29. Date indicator: ☐

(Complete only if date of diagnosis unknown)

30. Number of affected pregnancies before index date: ☐☐

31. Recorded diagnosis of hypertension when not pregnant before index date? ☐

(Defined as: elevated blood pressure treated by medication at any time before the index date)

1. Yes
0. No

32. Date 1st commenced anti-hypertensive medication: ☐☐ ☐☐ ☐☐

(If unknown, enter date that history of anti-hypertensive treatment 1st recorded and enter '1' in date indicator box)

33. Date indicator: ☐

(Complete only if date that commenced treatment unknown)

34. Recorded diagnosis of myocardial infarction (MI) before the index date? ☐

1. Yes
0. No

35. Date of 1st MI: ☐☐ ☐☐ ☐☐

(If unknown, enter date that history of MI 1st recorded and enter '1' in date indicator box)

36. Date indicator: ☐

(Complete only if date of diagnosis unknown)

37. Number of recorded episodes of MI before index date:

1. 1
2. 2
3. ≥ 3
4. Not recorded

38. Recorded diagnosis of angina before index date?

1. Yes
0. No

39. Date of 1st episode of angina:

(If unknown, enter date that history of angina 1st recorded and enter '1' in date indicator box)

40. Date indicator:

(Complete only if date of diagnosis unknown)

41. Recorded diagnosis of stroke before index date?

1. Yes
0. No

42. Date of 1st stroke:

(If unknown, enter date that history of stroke 1st recorded and enter '1' in date indicator box)

43. Date indicator:

(Complete only if date of diagnosis unknown)

44. Number of recorded strokes before index date:

1. 1
2. 2
3. ≥ 3
4. Not recorded

45. Recorded diagnosis of transient ischaemic attack (TIA) before index date

1. Yes
0. No

46. Date of 1st TIA:

(If unknown, enter date that history of TIA 1st recorded and enter '1' in date indicator box)

47. Date indicator:

(Complete only if date of diagnosis unknown)

48. Recorded diagnosis of other heart or blood vessel disease before index date?

1. Yes
0. No

49. Nature of heart or blood vessel disease:

1. Known cardiac valvular abnormality and / or clinically significant murmur *(e.g. requiring antibiotic prophylaxis)*
2. Murmur, not otherwise specified
3. Arrhythmia
4. Palpitations, not otherwise specified
5. Peripheral vascular conditions, arterial
6. Cardiac arrest, not otherwise specified
7. Surgery for congenital heart condition
8. Other arterial disease, excluding peripheral vascular disease
9. Hyperlipidaemia, treated by medication
10. Heart failure
11. Other

50. Nature of heart or blood vessel disease:

(Use this cell if a 2nd heart or blood vessel disease was recorded)

51. Recorded diagnosis of diabetes mellitus before index date?

1. Yes
0. No

52. Date diabetes mellitus 1st diagnosed:

(If unknown, enter date that history of diabetes 1st recorded and enter '1' in date indicator box)

53. Date indicator:

(Complete only if date of diagnosis unknown)

54. Type of diabetes:

1. Insulin-dependent
2. Non- insulin-dependent
3. Non- insulin-dependent, progressing to insulin-dependence
4. Pregnancy-induced diabetes only
5. Not recorded

55. Recorded diagnosis of blood disorders before index date?

1. Yes
0. No

56. Type of blood disorder:

1. Factor V Leiden
2. Antithrombin deficiency
3. Protein C deficiency
4. Protein S deficiency
5. Dysfibrinogenaemia
6. Plasminogen deficiency
7. Prothrombin G20210A
8. Elevated factor VIII concentration
9. Elevated platelet count (chronic)
10. Elevated platelet count (transient)
11. Homocysteinaemia
12. Antiphospholipid syndrome / anticardiolipin antibodies / lupus anticoagulant
13. Polycythaemia (chronic)
14. Polycythaemia (transient)
15. Other

57. Type of blood disorder:

(Use this cell if a 2nd blood disorder was recorded)

58. Type of blood disorder:

(Use this cell if a 3rd blood disorder was recorded)

59. Recorded diagnosis of cancer before the index date?

(Including current and past disease)

1. Yes
0. No

60. Date cancer 1st diagnosed: | | | | | | |

(If unknown, enter date that history of cancer 1st recorded and enter '1' in date indicator box)

61. Date indicator: |

(Complete only if date of diagnosis unknown)

62. Type of cancer: |

1. **Breast**
2. **Cervical**
3. **Uterine**
4. **Ovarian**
5. **Prostate**
6. **Bowel**
7. **Lung**
8. **Other**

63. Type of cancer: |

(Use this cell if a 2nd primary cancer was recorded)

64. Type of cancer: |

(Use this cell if a 3rd primary cancer was recorded)

65. Record of prolonged immobility during year before index date? |

(Defined as: confined to wheelchair, or documented confinement to bed or chair for at least a week)

1. **Yes**
0. **No**

66. Record of prolonged immobility during 2 months before index date? |

1. **Yes**
0. **No**

67. Record of travel of at least 4 hours' duration during 2 months before index date?

1. Yes
0. No

68. Number of recorded journeys of at least 4 hours' duration:

1. 1
2. 2
3. ≥ 3
4. Not recorded

69. Mode of transport used for journey(s):

1. Air
2. Car
3. Bus
4. Train
5. Other
6. More than one mode of transport used
7. Not recorded

70. Record of injuries requiring medical attention during year before index date?

(Include only: fractures of hip / pelvis / lower limb; severe soft tissue trauma lower limb; fractures or severe trauma trunk / head / neck / upper limb)

1. Yes
0. No

71. Record of injuries requiring medical attention during 2 months before index date?

1. Yes
0. No

72. Record of operations during year before index date? ☐

(Include only: major general, urological, gynaecological, cardiothoracic, vascular, orthopaedic, or neurological surgery)

1. Yes
0. No

73. Record of operations during 2 months before index date? ☐

1. Yes
0. No

74. Record of hysterectomy before index date? ☐

(Leave blank if male)

1. Yes
0. No

75. Date of hysterectomy: ☐☐ ☐☐ ☐☐

(If unknown, enter date that history of hysterectomy 1st recorded and enter '1' in date indicator box)

76. Date indicator: ☐

(Complete only if date of hysterectomy unknown)

77. Record of bilateral oophorectomy before index date? ☐

(Leave blank if male)

1. Yes
0. No

78. Date of oophorectomy: ☐☐ ☐☐ ☐☐

(If unknown, enter date that history of oophorectomy 1st recorded and enter '1' in date indicator box)

79. Date indicator:

(Complete only if date of oophorectomy unknown)

80. Record of intellectual disability before index date?

1. Yes
0. No

81. Duration of disability:

1. Since childhood
0. Since event in adulthood

82. Recorded diagnosis of psychiatric illness before index date?

1. Yes
0. No

83. Details of psychiatric history:

1. Diagnosis and treatment of a psychotic illness by a psychiatrist (as an inpatient)
2. Diagnosis and treatment of a psychotic illness by a psychiatrist (as an outpatient only)
3. Diagnosis and treatment of a psychotic illness by a general practitioner only
4. Diagnosis and treatment of another psychiatric illness by a psychiatrist (as an inpatient)
5. Diagnosis and treatment of another psychiatric illness by a psychiatrist (as an outpatient)
6. Diagnosis and treatment of another psychiatric illness by a general practitioner only

84. Details of psychiatric history:

(Use this cell if a 2nd psychiatric illness was recorded)

85. Record of any other relevant history before index date?

1. Yes
0. No

86. Details of other relevant conditions before index date:

1. Inflammatory bowel disease
2. Systemic lupus erythematosus
3. Renal disease
4. Other

87. Details of other relevant conditions before index date:

(Use this cell if a 2nd significant condition was recorded)

88. Record of pregnancy before index date?

(Leave blank if male)

1. Yes
0. No

89. Total number of recorded pregnancies before index date:

90. Number of recorded miscarriages before index date:

91. Number of recorded terminations of pregnancy before index date:

92. Number of recorded ectopic pregnancies before index date:

93. Number of recorded live births before index date:

94. Number of recorded stillbirths before index date: ☐☐

95. Number of pregnancies for which outcome was not recorded: ☐☐

96. Did any of the above pregnancies occur in year before index date? ☐

1. Yes
0. No

97. If pregnant during year before index date, estimated date of last menstrual period: ☐☐ ☐☐ ☐☐

If date unknown, record 1/1/49

98. If pregnant during year before index date, date that pregnancy ended: ☐☐ ☐☐ ☐☐

If date unknown but pregnancy known, or assumed (because of expected date of delivery), to have ended more than 2 months before the index date, record 1/1/50

If notes clearly indicate that was pregnant at any time during the 2 months before the index date, and unless have a known date that pregnancy ended, record 1/1/51

If no record of pregnancy status during 2 months before index date, but it is possible (because of expected date of delivery) that was pregnant during this time, record 1/1/52

99. Record of smoking status before index date? ☐

1. Yes
0. No

100. Smoking status: ☐

1. Smoker
2. Ex-smoker
3. Non-smoker

101. Date smoking status recorded: | | | | | | |

102. Record of being post-menopausal before index date? |

(Leave blank if male)

1. Yes
0. No

103. If known to be post-menopausal, was menopause natural? |

1. Yes
0. No

104. Date of last menstrual period or surgery: | | | | | |

(If unknown, enter date that post-menopausal status 1st recorded and enter '1' in date indicator box)

105. Date indicator: |

(Complete only if date of last menstrual period or surgery unknown)

106. If not known to be post-menopausal, record of peri-menopausal symptoms before index date? |

1. Yes
0. No

107. Record of hormone replacement therapy (HRT) before index date? |

(Defined as: use of systemically absorbed oestrogen with or without progestogen, including use by men)

1. Yes
0. No

108 - 159. Details of HRT:

(Each row represents an episode of continuous HRT ordered from the most, to the least, recent)

(i) Regimen	(ii) Date episode of use began	(iii) Date episode of use ended	(iv) Current use?

(i) Regimen:

1. **Oestrogen alone**
0. **Combined oestrogen and progestogen**

(ii) Date this episode of HRT began

(Date of 1st prescription)

(iii) Date this episode of HRT ended

(Calculate using date of final prescription plus number of months prescribed on that occasion; or record index date if was still using HRT on the index date)

(iv) Current use?

(Part, or all, of this episode of use occurred in the 3 months before the index date)

1. Yes
0. No

160 - 181. Recorded use of the following methods of contraception?

	(i) Before the year of interest	(ii) In the year before index date
Oral contraceptives (OC) *(including for non-contraceptive indications)*	☐	☐
Progestogen-only pill	☐	☐
Medroxyprogesterone acetate (DMPA)	☐	☐
Morning after pill	☐	☐
Intrauterine device (IUD)	☐	☐
Diaphragm	☐	☐
Condoms	☐	☐
Female sterilisation	☐	☐
Partner vasectomy	☐	☐
Natural family planning	☐	☐
Other	☐	☐

1. Yes
0. No
2. Not applicable, post-menopausal
3. Not relevant, male

182 - 191. Details of contraception used in the year before index date (excluding OC use):

(Each row represents a contraceptive method ordered from the most, to the least, recently used)

(i) Method **(ii) Current use?**

(i) Method:

1. **Progestogen-only pill, 28x Ethynodiol diacetate 500µg (Femulen)**
2. **Progestogen-only pill, 28x Levonorgestrel 30µg (Microlut, Microval)**
3. **Progestogen-only pill, 28x Norethisterone 350µg (Noriday)**
4. **Progestogen-only pill, not otherwise specified**
5. **DMPA**
6. **Morning after pill**
7. **IUD**
8. **Diaphragm**
9. **Condoms**
10. **Female sterilisation**
11. **Partner vasectomy**
12. **Natural family planning**
13. **Other**

(ii) Current use?

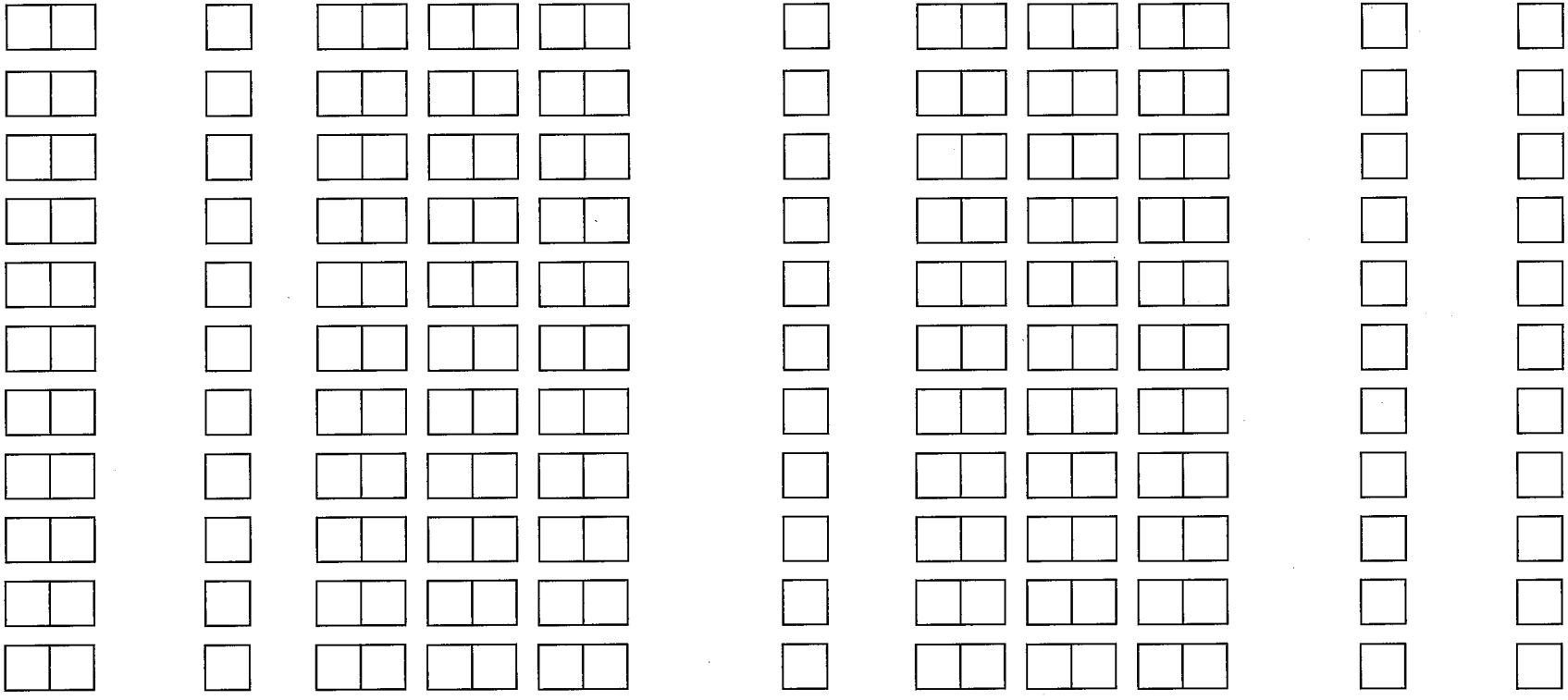
(Part, or all, of this episode of use occurred in the 3 months before the index date)

1. **Yes**
0. **No**
2. **Possible**

192 - 268. Details of OC use (ever):

(Each row represents an episode of continuous OC use ordered from the most, to the least, recent)

(i) Preparation | **(ii) 1st extra data column** | **(iii) Date this episode of use began** | **(iv) 2nd extra data column** | **(v) Date this episode of use ended** | **(vi) Use in year before index date?** | **(vii) Current use?**



(i) Preparation

1. **21x Desogestrel 150µg / Ethinyloestradiol 20µg tablets (MERCILON)**
2. **21x Desogestrel 150µg / Ethinyloestradiol 30µg tablets (MARVELON)**
3. **7x Desogestrel 25µg / Ethinyloestradiol 40µg tablets;**
   15x Desogestrel 125µg / Ethinyloestradiol 30µg tablets (GRACIAL)
4. **21x Gestodene 75µg / Ethinyloestradiol 30µg tablets (FEMODENE, MINULET)**
5. **21x Levonorgestrel 100µg / Ethinyloestradiol 20µg tablets (LOETTE)**
6. **21x Levonorgestrel 150µg / Ethinyloestradiol 30µg tablets (MICROGYNON 30, NORDETTE, MONOFEME)**
7. **21x Levonorgestrel 125µg / Ethinyloestradiol 50µg tablets (MICROGYNON 50)**
8. **MICROGYNON not otherwise specified**
9. **21x Levonorgestrel 250µg / Ethinyloestradiol 50µg tablets (NORDIOL, NEOGYNON)**
10. **11x Levonorgestrel 50µg / Ethinyloestradiol 50µg tablets;**
    10x Levonorgestrel 125µg / Ethinyloestradiol 50µg tablets (BIPHASIL)
11. **6x Levonorgestrel 50µg / Ethinyloestradiol 30µg tablets;**
    5x Levonorgestrel 75µg / Ethinyloestradiol 40µg tablets
    10x Levonorgestrel 125µg / Ethinyloestradiol 30µg tablets (TRIPHASIL, TRIQUILAR, TRIFEME)
12. **21x Norethisterone 500µg / Ethinyloestradiol 35µg tablets (NORIMIN, BREVINOR)**
13. **21x Norethisterone 1000µg / Ethinyloestradiol 35µg tablets (BREVINOR-1)**
14. **21x Norethisterone acetate 1000µg / Ethinyloestradiol 50µg tablets (ORLEST)**
15. **21x Norethisterone acetate 2500µg / Ethinyloestradiol 50µg tablets (NORLESTRIN 28)**
16. **21x Norethisterone acetate 3000µg/ Ethinyloestradiol 50µg tablets (GYNOVLAR)**
17. **21x Norethisterone acetate 4000µg / Ethinyloestradiol 50µg tablets (ANOVULAR)**
18. **7x Norethisterone 500µg / Ethinyloestradiol 35µg tablets;**
    9x Norethisterone 1000µg / Ethinyloestradiol 35µg tablets;
    5x Norethisterone 500µg / Ethinyloestradiol 35µg tablets (SYNPHASIC)
19. **21x Norethisterone 1000µg / Mestranol 50µg tablets (NORINYL-1)**
20. **21x Norgestrel 500µg / Ethinyloestradiol 50µg tablets (OVRAL)**
21. **21x Ethynodiol diacetate 500µg / Ethinyloestradiol 50µg tablets (OVULEN 0.5/50)**
22. **21x Ethynodiol diacetate 1000µg / Ethinyloestradiol 50µg tablets (OVULEN 1/50, EDULEN)**
23. **OVULEN not otherwise specified**
24. **21x Lynoestrenol 750µg / Ethinyloestradiol 38µg tablets (RESTOVAR)**
25. **22x Lynoestrenol 1000µg / Ethinyloestradiol 50µg tablets (OVOSTAT)**
26. **21x Lynoestrenol 2500µg / Mestranol 75µg tablets (LYNDIOL 2.5)**
27. **LYNDIOL not otherwise specified**
28. **21x Norgestrel 500µg / Ethinyloestradiol 50µg tablets (EUGYNON)**
29. **21x Megestrol acetate 100µg / Ethinyloestradiol 100µg tablets (SERIAL C)**
30. **21x Megestrol acetate 4000µg / Ethinyloestradiol 50µg tablets (VOLIDAN)**
31. **21x Norethynodrel 5000µg / Mestranol 150µg tablets (ENAVID)**
32. **15x Chlormadinone acetate 2000µg / Mestranol 80µg tablets; 5x Chlormadinone acetate 2000µg / Mestranol 80µg tablets (SEQUENS)**
33. **21x Cyproterone acetate 2000µg / Ethinyloestradiol 35µg tablets (DIANE)**
34. **ORAL CONTRACEPTIVE not otherwise specified**

(ii) 1st extra data column

1. **e.g. Nov 97**
2. **e.g. 6 months**

(iii) Date this episode of OC use began

(Date of 1st prescription)

(iv) 2nd extra data column

1. **e.g. Nov 97**
2. **e.g. pre-Dec 96**

(v) Date this episode of OC use ended

(Calculate using date of final prescription plus number of months prescribed on that occasion; or record index date if still an OC user on the index date)

(vi) Use in year before index date?

(Part, or all, of this episode of use occurred in the year before the index date)

1. **Yes**
0. **No**
2. **Possible**

(vii) Current user?

(Part, or all, of this episode of use occurred in the 3 months before the index date)

1. **Yes**
0. **No**
2. **Possible**

269. Any other medication prescribed in the year before the index date? ☐

1. Yes
0. No

270 - 385. Details of other medication prescribed in the year before the index date:

(i) Medication *Prefix*	*Suffix*	(ii) Indication for treatment	(iii) Current use?
☐☐	☐☐☐	☐☐	☐
☐☐	☐☐☐	☐☐	☐
☐☐	☐☐☐	☐☐	☐
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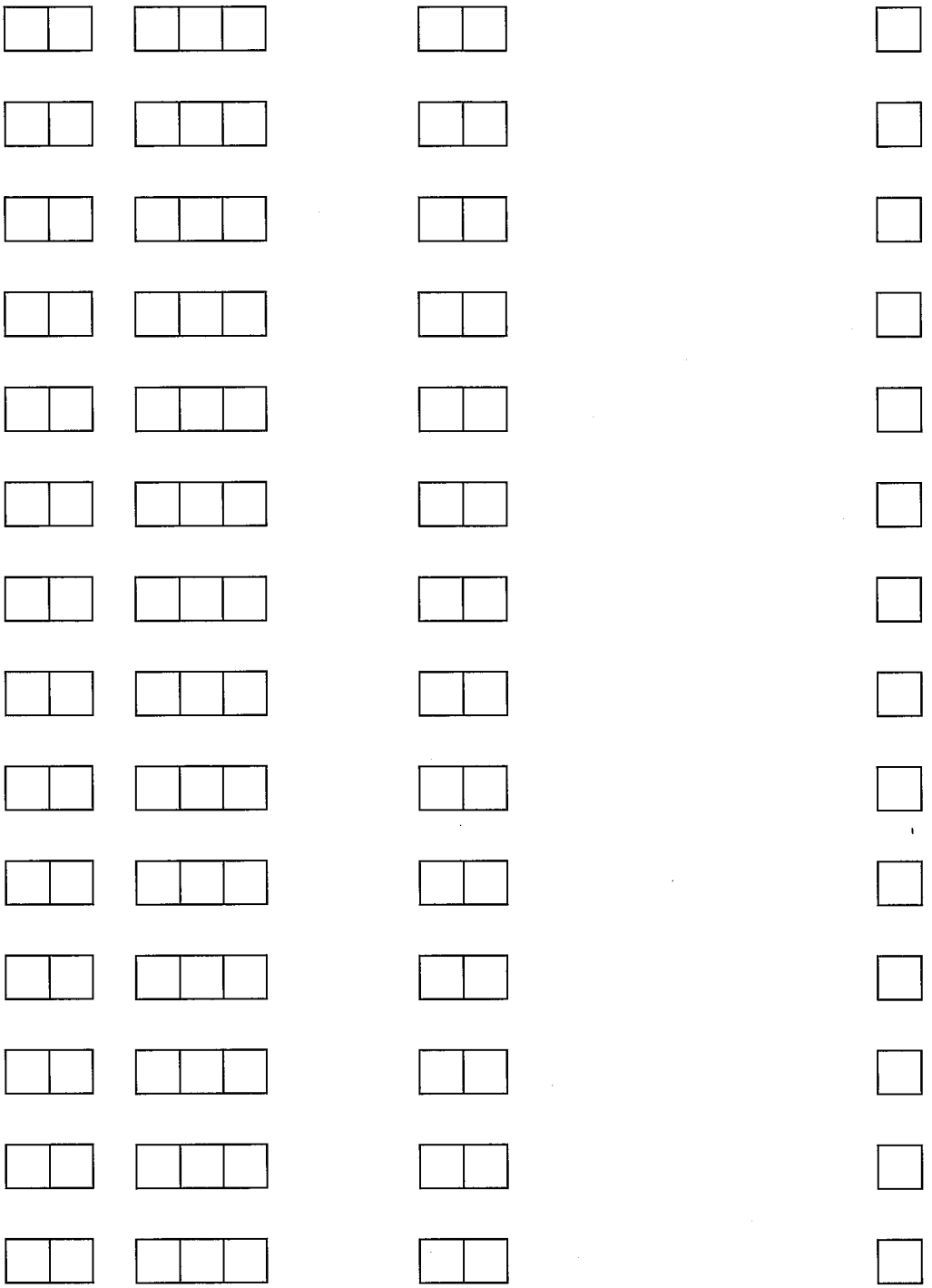
☐☐	☐☐☐	☐☐	☐



(i) Medication code:

(As per drug dictionary from Centre for Adverse Reactions Monitoring)

(ii) Indication for treatment:

1. **Hypertension**
2. **Heart failure**
3. **Ischaemic heart disease**
4. **Oedema not otherwise specified**
5. **Insulin dependent diabetes**
6. **Non-insulin dependent diabetes**
7. **Systemtic lupus erythematosus**
8. **Inflammatory bowel disease**
9. **Other gastrointestinal conditions**
10. **Renal failure**
11. **Renal transplant**
12. **Depression**
13. **Psychotic illness**
14. **Anxiety or insomnia**
15. **Asthma**
16. **Chest infection**
17. **Upper respiratory tract infection**
18. **Soft tissue infection lower limbs**
19. **Infection other sites, including infection prophylaxis**
20. **Infection, not otherwise specified**
21. **Peri-menopausal symptoms, excluding abnormal vaginal bleeding**
22. **Abnormal vaginal bleeding**
23. **Epilepsy**
24. **Migraine**
25. **Hyperthyroidism**
26. **Hypothyroidism**
27. **Obesity**
28. **Thrombotic disorders**
29. **Pain**
30. **Other conditions**

(iii) Current user of this medication?

(Part, or all, of this episode of use occurred in the 3 months before the index date)

1. **Yes**
0. **No**
2. **Possible**

386. Any record of weight before index date? ☐

(Measured weight or comment about weight)

1. Yes
0. No

387. Date of latest weight measurement before index date: ☐☐ ☐☐ ☐☐

(Or date of comment if not measured)

388. Circumstances when weight recorded: ☐

1. Female, not pregnant
2. Female, first trimester of pregnancy
3. Female, second or third trimester of pregnancy
4. Female, ≤ 6 weeks post-partum
5. Male

389. Weight in kilograms: ☐☐☐ ☐

390. Weight in stones and pounds: ☐☐ ☐☐

391. Narrative comments about weight: ☐

(Record only if weight was not measured)

1. Overweight
2. Average weight
3. Underweight

392. Any record of height before index date? ☐

(Measured height or comment about height)

1. Yes
0. No

393. Date of latest height measurement before index date:

(Or date of comment if not measured)

394. Height in metres:

395. Height in feet and inches:

396. Narrative comments about height:

(Record only if height was not measured)

1. Above average height
2. Average height
3. Below average height

397. Any recorded family history of venous thromboembolism before index date?

1. Yes
0. No

398 - 401. Relationship to case:

(Each row represents a family member with a history of venous thromboembolism)

1. Parent
2. Sibling
3. Child
4. Aunt or uncle
5. Grandparent
6. Other
7. Not specified

APPENDIX C: CASE REPORTS AND CASE SERIES DESCRIBING VENOUS THROMBOEMBOLISM IN AIR TRAVELLERS

Table Case reports and case series describing venous thromboembolism following travel by air

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Homans 1954)	5 patients diagnosed with DVT over a 13-year period, source not stated.	4 (non-fatal)	3 men, 1 woman. Median age 53.5 years (range 19 – 56)	Aeroplane (2). Car (2).	Only stated for one case (14 hours).	During or immediately after travel (2), 2 hours (1), 4 days (1).
(Beighton and Richards 1968)	25 consecutive patients who were admitted directly to Hillingdon Hospital from Heathrow Airport, in the years 1963 to 1965, after suffering a cardiovascular event during or immediately after a flight.	1 (fatal)	49 year old "previously healthy" woman developed DVT and subsequently died from cerebral embolism following the passage of clot through a patent foramen ovale.	Aeroplane (1).	Not stated, although was noted to be Australian.	On arrival.
(Symington and Stack 1977)	182 patients with PE who were admitted to hospitals in Glasgow over a 3-year period.	8 (non-fatal)	5 men, 3 women. Median age 54 years (range 30 – 84). 6 cases had a history of "venous disorders of the legs".	Aeroplane (3), all in economy class. Car (3). Train (1). Train/ship (1).	Median 9.5 hours (range 3 – 24).	Median 48 hours (range 2 – 96).
(Line and Whitaker 1979)	1 patient with PE who was admitted to a hospital in the UK.	1 (non-fatal)	29 year old man, very fit and active.	Aeroplane (1).	Was a pilot who always flew ≥ 3 hours.	Not stated.
(Thomas et al. 1981)	1 patient with PE who was admitted to a hospital in Zimbabwe.	1 (non-fatal)	49 year old man, no risk factors.	Aeroplane (1), economy class	29 hours.	On arrival.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Marshall 1982)	1 patient with DVT who was admitted to a hospital in Munich.	1 (non-fatal)	32 year old woman.	Aeroplane (1).	8 hours.	24 hours.
(Ledermann and Keshavarzian 1983)	3 patients with PE who were admitted directly to Hillingdon Hospital from Heathrow Airport during an undefined period.	3 (1 fatal)	3 women. Median age 63 years (range 59 – 66). 1 case had metastatic carcinoma of the breast, another was obese. None had a history of "venous disease".	Aeroplane (3).	All 3 flew from Southern Hemisphere (Australia, New Zealand, Zimbabwe).	On arrival.
(Hart et al. 1985)	1 patient with PE who was admitted directly to Ashford Hospital from Heathrow Airport.	1 (non-fatal)	39 year old woman. Symptoms of mild gastroenteritis immediately before and during flight. No other risk factors.	Aeroplane (1).	27 hours.	On arrival.
(Holliday 1985)	1 patient with PE who was admitted to hospital 19 days after flight.	1 (non-fatal)	44 year old man, mildly obese, "otherwise in good health".	Aeroplane (1).	15 hours.	2 weeks.
(Alberty-Ryöppy et al. 1985)	1 patient with DVT who was admitted Helsinki University General Hospital.	1 (non-fatal)	32 year old "previously healthy" woman.	Aeroplane (1).	12 hours.	On arrival.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Sarvesvaran 1986)	104 sudden deaths reported to the coroner, between February 1979 and January 1982, which occurred in Heathrow Airport or on a flight terminating at the Airport (61 in-flight, 28 would-be passengers, 15 staff or non-travelling spectators). 11/61 (18%) of in-flight deaths were due to PE, compared with 1/28 (4%) of deaths among would-be passengers)	11 (all fatal)	2 men, 9 women. Ages not given. 8 cases reported to have no significant medical history, details of risk factors of remaining cases not discussed.	Aeroplane (11).	1 passenger died during a 6 – 12 hour flight, 10 died during 12 – 18 hour flights.	During flight.
(Cruickshank et al. 1988)	6 patients with PE, 2 of whom were authors of the paper. The source of the other patients was not described.	6 (non-fatal)	5 men, 1 woman Median age 49.5 years (range 31 – 79). 3 cases considered to have predisposing conditions: acute nephritic syndrome and dehydration (1), CHF (1) previous athletic injury 7 and 2 years earlier (1).	Aeroplane (6), at least 1 case (an author) travelled in business class.	7 hours (1), 10 hours (1), 24 hours (1). Flight duration not reported for other 3 cases: UK to Asia and multiple trips within Asia over a 4-week period (1), Washington to London (1), UK to USA (1).	Median 1 day (range: during flight and up to 10 days after arrival).
(Finch et al. 1988)	2 patients with PE who were admitted directly to Ashford Hospital from Heathrow Airport over a 3-week period.	2 (both fatal)	66 year old man, overweight, hypertensive, smoker. 84 year old woman, usually well.	Aeroplane (2).	Thailand to UK. China to UK.	On arrival. During flight.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(O'Donnell 1988)	250 patients with VTE who were admitted to Freemantle Hospital in Western Australia over a 3-year period. 8 air travellers. Another 5 had undertaken "lengthy" (undefined) trips by road but the characteristics of these patients were not described.	8 (1 fatal)	2 men, 6 women. Mean age 61 years (range 38 – 80). Risk factors (no of cases): malignancy (1), previous DVT (1), obesity (1), smoker (3). Unclear whether 6 cases had risk factors or whether some cases had > 1 risk factor.	Aeroplane (8).	Flights to Western Australia from: Europe (6), Africa (1), Asia (1).	Not specifically stated - admitted to hospital after "recently" arriving in Australia.
(Bürki 1989)	2 patients (sisters) with DVT (1) and PE (1).	2 (1 fatal)	25 year old woman, overweight, OC, post-splenectomy thrombocytosis, strong family history of PE. 31 year old woman, overweight, OC, splenectomy, family history as above.	Aeroplane (2).	11 hours (1). Switzerland to Australia (1).	During flight (both).
(Steinhauser and Stewart 1989)	3 USA Air Force pilots who were admitted to hospital with DVT between 1984 and 1987.	3	3 men aged 30, 32, and 36 years. Risk factors (no of cases): previous post-operative mesenteric venous thrombosis (1), soft tissue knee injury (1).	Aeroplane (3).	5 hours (1), not stated for others.	At end of journey (1), not stated for others.
(Voorhoeve and Bruyninckx 1990)	1 patient with DVT and 1 with PE, source not stated.	2 (non-fatal)	68 year old woman. 44 year old man.	Car (1). Aeroplane (1).	Italy to the Netherlands by car (1), trans-Atlantic flight (1).	At end of car journey. 2 weeks after flight.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Benoit 1992)	12 patients with DVT ± PE who were admitted to hospital in Geneva during an undefined period.	12 (non-fatal)	8 men, 4 women Median age 47 years (range 23 – 71). 10/12 cases had ≥ 1 pre-existing risk factors for VTE Risk factors (no of cases): previous VTE (5), family history of VTE (2), varicose veins (1), diarrhoea and dehydration (1), OC (1), CHF (1), > 1.8m tall (6).	Aeroplane (9). Aeroplane and car (1). Car (1). Train (1).	Median 11.5 hours (range 3 – 40)	Median 2 hours (on arrival – 15 h)
(Schmitt and Mihatsch 1992)	54 consecutive patients diagnosed with isolated thrombosis of popliteal vein at the Cardiovascular Radiology Department of the University of Basel, Switzerland.	14 (outcome not stated)	No details provided.	Aeroplane. Bus. (Numbers not provided).	No details provided.	No details provided.
(Black 1993)	1 patient (the author) admitted to hospital with DVT following a long-distance flight. Twenty years later he developed PE after a flight.	1 (non-fatal)	1 man, age and other characteristics not described.	Aeroplane (1).	1st episode: Trans-Atlantic flight from USA to UK. 2nd episode: "overnight flight in cramped conditions"	1st episode: 10 days. 2nd episode: 1 week.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Sahiar and Mohler 1994)	1 patient admitted to hospital with DVT in left leg.	1 (non-fatal)	61 year old man. Elective proximal tibial osteotomy of left knee six weeks earlier, plaster cast removed on day of flight.	Aeroplane (1), economy class.	Domestic flight within USA (Rochester to Oklahoma City), duration not stated.	During flight.
(Levy et al. 1995)	1 patient admitted to hospital with PE and 1 admitted with thrombosis of the femoral vein.	2 (non-fatal)	46 year old man, no risk factors. 72 year old man, laryngeal malignancy 20 years earlier	Aeroplane (2).	10 hours. 16 hours.	3 days. "Several days".
(Paganin et al. 1996)	6 patients admitted to hospital with PE after flights from Paris to Réunion Island over a 1-year period.	6 (non-fatal)	3 men, 3 women. 2 severe cases aged 58 and 59 years, mean age of others was 62 years (SD 3.1). Only risk factor among cases was HRT (taken by 1 woman).	Aeroplane (6), at least 5 in economy class.	12 hours.	Median 42 hours (range: on arrival up to 4 days after arrival).

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Eklof et al. 1996)	Retrospective review of records of 254 patients with DVT ± PE, who were admitted to Straub Hospital, Honolulu, between January 1988 and December 1993. Not stated whether all patients were asked about travel, but the records of 44 documented air travel up to 6 weeks before admission.	44 (non-fatal)	24 men, 20 women. Mean age 63 years (range 32 – 86). 37/44 (84.1%) cases had ≥ 1 pre-existing risk factors for VTE: 1 risk factor (32), 2 risk factors (5). Risk factors (no of cases): previous DVT (15), malignancy or chronic illness (11), HRT or OC (7), minor to moderate lower limb injuries < 2 weeks earlier (5), recent surgery (2), femoral catheterisation < 3 weeks earlier (2).	Aeroplane (44).	5 – 17 hours, no other information given.	During flight (2), < 1 week (37), 1 – 4 weeks (3), 5 – 6 weeks (2).
(Emonson 1997)	1 patient admitted to hospital with DVT.	1 (non-fatal)	28 year old man, FVL mutation, family history of DVT (sister and both maternal grandparents).	Aeroplane (1).	Not stated, was a navigator with the Royal Australian Air Force.	4 days.
(Nissen 1997)	1 patient with DVT and 4 with PE who were admitted to a German hospital.	5 (non-fatal)	1 woman, sex of others not stated. Median age 57 years (range 51 – 60). Risk factors (no of cases): essential thrombocytosis (1), FVL mutation (2), malignancy (1).	Aeroplane (4): business class (1), economy class (1). Car (1).	Flights: 2.5 hours (1), 4.5 hours (1), 20 hours (1), Germany to South East Asia (1). Car: 8.5 hours (1).	2 days – 4 weeks.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Barker et al. 1997)	President of the USA who developed DVT on 3 occasions after long-distance flights.	1 (non-fatal)	52 years when developed first DVT.	Presidential aeroplane (1).	USA to Japan, to the Middle East, and to Russia.	Not stated.
(Ribier et al. 1997)	40 patients with DVT ± PE who were admitted to hospital in Martinique between 1989 and 1995.	40 (non-fatal)	11 men, 29 women. Mean age 55.8 years (range 19 – 84). Risk factors (no of cases): previous VTE (12 cases, 6 were flight-related), chronic disease (4), malignancy (2), OC (7), recent surgery (9).	Aeroplane (40).	4 hours (2), 8 – 9 hours (34), not stated (4).	On arrival (9), < 24 hours (13), 1 – 3 days (2), 4 – 28 days (16).
(Mercer and Brown 1998)	Retrospective review of records of 134 patients with DVT ± PE, who were admitted to the Tripler Army Medical Center, Honolulu, over a 4-year period. Documented enquiry about air travel in the records of 66 patients. 41/66 had flown ≤ 6 months before onset of symptoms, but only those who had flown within 31 days of the onset of symptoms (33/44) were described further.	33 (7 fatal)	27 men, 6 women. Median age 48 years (range 19 – 80). 21/33 (63.6%) cases had ≥ 1 pre-existing risk factors for VTE: 1 risk factor (19), 2 risk factors (1), 3 risk factors (1). Risk factors (no of cases): previous VTE (7), anti-cardiolipin antibody (2), malignancy (7), CHF (4), recent leg surgery (1), paraplegia (1), "oestrogen therapy" (1), not stated (1).	Aeroplane (33).	Minimum flight time was 4 hours. 24 patients had flown to Honolulu from unspecified North American airports, 8 from Asia, and 1 from South America.	Time from start of flight to symptoms: median 4 days (range: during flight – 31 days).

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Rege et al. 1999)	Retrospective review of records of patients with DVT referred to the anticoagulation clinic St George's Hospital in London over a 3-year period. Identified 20 patients who had spontaneously reported that they had flown at some time in the 35 days before the onset of symptoms.	20 (non-fatal)	5 men, 15 women. Median age 40 years (22 – 66). 15/20 (75%) cases had ≥ 1 pre-existing risk factors for VTE: 1 risk factor (7), 2 risk factors (5), 3 risk factors (3). Risk factors (no of cases): previous thrombosis (4), FVL mutation (5), protein S deficiency (1), OC use (5), HRT (2), puerperium (1), malignancy (1), injury to affected leg (2), pneumonia (1), family history of VTE (4).	Aeroplane (20): business class (2), economy class (18).	Median 7 hours (range 1 – 23).	Median 2 days (range 0 – 35).
(Clerel and Caillard 1999)	70 patients with PE seen by the medical department at Aeroports De Paris between 1984 and 1998 after arrival at Charles de Gaulle or Orly airports. The characteristics of 64 patients who arrived between 1990 and 19 98 were described.	64 (non-fatal)	15 men, 49 women. Median age 59.5 years (range 26 – 85).	Aeroplane (64): first class (3), business class (1), economy class (44), class not determined (16).	Median 13 hours (range 3 – 23).	Before left airport.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Sinzinger et al. 1999)	19 patients referred to a thrombosis centre in Austria over an 18-month period for diagnostic investigations, thrombophilia screening, and other coagulation tests. 15/19 had objective evidence of VTE (all PE). 15/19 travelled by air.	15 (non-fatal)	14 men, 1 woman. Median age 50 years (range 33 – 75). Risk factors (no of cases): overweight (5), diarrhoea at time of flight (4), fever and influenza symptoms (5). None had a history of VTE, a chronic disease, or abnormalities of the coagulation or prostaglandin systems.	Aeroplane (15): first class (1), economy class (14).	Median 9 hours (range 5 – 22).	Median 20 hours (range: during flight – 85 hours)
(Simon 1999)	77 patients with DVT, 39 with PE.	77 (non-fatal)	41/77 (53.2%) cases had $\geq$ 1 pre-existing risk factors for VTE.	Aeroplane (77).	Mean 12 hours.	Mean 3.1 days.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Arfvidsson et al. 1999)	109 consecutive patients with DVT ± PE admitted to Straub Hospital, Honolulu, between July 1995 and October 1998. In contrast to the earlier case series from this hospital, all the patients were asked about "recent" (undefined) air travel, as well as other risk factors for VTE, while they were still in hospital.	25 (non-fatal)	11 men, 14 women. Mean age 58 years (range 36 – 79). 23/25 (92%) cases had ≥ 1 pre-existing risk factors for VTE. Mean no of risk factors was 3. Risk factors (no of cases): previous VTE (7), HRT (6), OC (1), overweight or obese (19), malignancy (7), recent lower limb injury (4), recent surgery for malignancy (3), chronic heart disease (11), other chronic disease (8).	Aeroplane (25).	Mean 9 hours (range 5 – 8).	Time from start of flight to symptoms: < 24 hours (20, including 9 cases who developed symptoms during flight), 1 – 7 days (3), 8 – 10 days (2).
(Parsi and McGrath 2000; Parsi et al. 2001)	64 patients who developed SVT, DVT, or PE ≤ 28 days after travel by air, car, train, or bus and were seen in the vascular laboratory at St Vincent's Hospital, Sydney, between 1996 and 1999.	64 (non-fatal)	32 men, 32 women. Median age 48 years. Risk factors (no of cases): previous VTE (24), thrombophilia (46), obesity (37), HRT or OC use (20), recent surgery or trauma (8), infection (5), malignancy (3), family history of VTE (19).	Aeroplane (58): first class (2), business class (12), economy class (42), cabin crew (2). Car or bus (4). Train (2).	Mean travel time by air: 23.4 hours (range 3 – 55). Mean travel time by car: 23.2 hours (range 11 – 44).	During flight (48), < 1 week (9), 1 – 4 weeks (7).

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Kesteven and Robinson 2001)	86 patients who developed DVT ± PE ≤ 28 days after air travel. Series included 18 patients (interviewed face-to-face) who were part of an ongoing regional study of VTE by researchers at the Freeman Hospital in Newcastle on Tyne and 68 people who responded to a notice in a national newspaper in March 1999 (initially completed a questionnaire and then were interviewed, presumably by telephone).	86 (non-fatal)	44 men, 42 women. Mean age 59 years (range 20 – 83). 62/86 (72%) cases had ≥ 1 pre-existing risk factors for VTE. Risk factors (no of cases): family history of VTE (17), HRT or OC (19), "≥ 1 other of the VTE risk factors examined" (26). BMI of the cases was reported to be no different from general population.	Aeroplane (86): business class (13), economy class (73).	"Up to 3 hours" (11). "3 – 6 hours" (12). "6 – 9 hours" (9). "9 – 12 hours" (17). "12 – 15 hours" (12). "15 – 18 hours" (8). "18 – 21 hours" (1). "21 – 24 hours" (11). "> 24 hours" (5). 75 had undertaken more than one flight.	During flight or < 24 hours (48), 24 – 96 hours (31), > 96 hours (7). 5 patients had mild leg symptoms before the flight which worsened during or after flight. Symptoms following an outbound flight in 29 (18 undertook sequential flights over several days).
(Partsch 2001)	543 consecutive patients with DVT ± PE admitted to Wilhelminen Hospital in Vienna between January 1996 and December 1998.	39 (non-fatal)	15 men, 24 women. Mean age 63.1 years (range not provided). Risk factors (no of cases): known malignancy (6), malignancy found on screening (2). No other comments.	Aeroplane (11). Car, bus, or train (28).	> 5 hours (39), no other details provided.	During, or directly after, a flight (2). No information given about remaining cases.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Cheung and Duflou 2001)	Retrospective review of medical records and histological slides of 14 of 15 passengers who died from PE on a flight that landed at Sydney International Airport (6) or within 2 hours of landing (8) over a 6-year period.	14 (fatal)	3 men, 11 women. Median age 68.5 years (range 54 – 76). Histological evidence of PE which commenced before boarding plane found in 4 cases. In 10 cases, histological changes consistent with fresh thrombus formed during flight.	Aeroplane (14): first or business class (2), economy class (12).	Median 15 hours (range 2 – 23).	During flight or within 2 hours of landing.
(Johnston and Evans 2001)	27 cases of VTE in pilots between 1990 and 2000 in UK, identified from Civil Aviation Authority Database. 16 cases followed trauma or surgery, 11 no obvious risk factors other than flying.	11 (non-fatal)	Population of healthy workers, mean age 39 years.	Aeroplane (16).	Not stated.	2 cases developed symptoms "shortly after" flights as passengers.
(Tan et al. 2002)	Retrospective review of the records of 42 consecutive patients with PE who were admitted to Changi General Hospital, near Changi International Airport, Singapore between October 1998 and May 2000.	9 (unclear whether any deaths)	8 air travellers were all Caucasian, no other details provided. 1 Chinese man who travelled by bus had protein S deficiency and a history of mesenteric venous thrombosis.	Aeroplane (8). Bus (1).	Mean 10.3 hours (range 5 – 15), included bus journey of 8 hours.	Air passengers: all transferred directly from airport to hospital. Bus passenger: not stated.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Kesteven and Robinson 2002)	1,250 consecutive patients with objectively confirmed DVT ± PE admitted to 5 hospitals within the area covered by two Health Authorities in the UK (Newcastle and North Tyneside, and Northumberland) between September 1998 and August 2000. Patients interviewed using a structured questionnaire within 4 weeks of diagnosis.	47 (not stated whether any deaths)	21 men, 26 women. Mean age 60 years (range 29 – 84). 44/47 (94%) cases had ≥ 1 pre-existing risk factors for VTE. Risk factors (no of cases): varicose veins (23), ≥ 1 "medical risk factor" (25), family history of VTE (11), HRT or OC (7), BMI > 30 kg/m² (8). 9/18 cases who were tested had thrombophilia.	Aeroplane (28), all in economy class. Car (11). Bus (6). Train (2).	Median 6 hours (range 2.5 – 30).	Time from start of journey to symptoms: during journey (20), ≤ 3 days (18), 4 – 7 days (4), 8 – 28 days (5).
(McQuillan et al. 2003)	Retrospective review of the records of an unstated number of consecutive patients with objectively confirmed DVT, PE, or superficial thrombophlebitis who presented to a Perth hospital or an affiliated private haematology clinic in Western Australia between July 1999 and April 2001.	58 (not stated whether any deaths)	30 men, 28 women. Median age 49.8 years (range 17 – 82). No of acquired or genetic risk factors (no of cases): none (9), 1 (19), 2 (21), ≥ 3 (9).	Aeroplane (48): PE (21), proximal DVT (17), 4 calf DVT (4), SVT (6). Car (7). Bus (3).	"< 4 hours" (7). "4 – 8 hours" (17). "8 – 12 hours" (10). "> 12 hours" (24).	Information available for 16 patients only: median 2.8 days, (range 0 – 28).
(O'Connell et al. 2005)	1 patient admitted to Christchurch Hospital in New Zealand with massive PE.	1 (non-fatal)	40 year old woman taking OC, BMI 29 kg/m².	Aeroplane (1).	At least 24 hours (UK to New Zealand).	During flight.

Reference	Cases	No of cases who developed VTE following travel	Characteristics of cases who developed VTE following travel	Mode of travel (no of cases)	Duration of travel	Elapsed time from end of journey to onset of symptoms
(Moghal and Krishnan 2005)	1 child with DVT.	1 (non-fatal)	13 year old girl from the UK who undertook a return trans-Atlantic trip, concurrent undiagnosed relapse of nephrotic syndrome. FVL mutation, maternal grandfather had a history of DVT.	Aeroplane (1).	Trans-Atlantic flight to and from UK.	2 weeks after second flight.
(Schreijer et al. 2005)	1 case of DVT.	1 (non-fatal)	33 year old woman who during a one month period undertook a return trip from the Netherlands to Nepal. FVL mutation, took a diuretic to prevent altitude sickness.	Aeroplane and bus (1).	2 flights of 12 hours, 2 bus trips of 6 and 12 hours.	Directly after return flight to the Netherlands.

`Abbreviations used in the table BMI: body mass index, CHF: congestive heart failure, DVT: deep vein thrombosis, FVL: factor V Leiden, HRT: hormone replacement therapy, m: metres, OC: oral contraceptive, PE: pulmonary embolism, UK: United Kingdom, USA: United States of America, VTE: venous thromboembolism.

APPENDIX D: CONSENT FORMS

Descriptive and case-control studies of long-distance air travel

Subject no. | | | | |

Consent Form 1: Next of kin who returned the contact details form

Name(s) of case _____

Name(s) of next of kin _____

Relationship to case _____

Address _____

_____

Telephone number _____

Hello, may I please speak to (*name of next of kin*)?
I am Lianne Parkin, a doctor from the Otago Medical School. Thank you very much for returning the form that I sent you. You said that this would be a good time to speak to you, is it still alright? ***(If yes, continue. If no, ask: when would you like me to ring back? Record date and time on page 2)*** As I said in the letter I sent you, we are carrying out a major study on the causes of pulmonary embolism. Our aim is to identify factors that could help in preventing deaths from this condition in the future. We are interviewing the relatives of people who have died from pulmonary embolism about their life and health before they became unwell. If you agree to take part in the study, all the information you give us will be recorded without names and will be kept strictly confidential. Also if you do not want to answer particular questions that is fine. Do you have any questions about the study that you wish to ask? Would you be willing to help by answering some questions about your (*relative's*) life and health for our study?

Consent: Obtained / Refused *1 = obtained 2 = refused* |

Signed: _____ **Date:**_____

Subject no. | | | | | |

If consent not given: Thank you very much for your time. Goodbye.

If consent given: I'd like to make a time for _____ to call you back for the telephone interview. It will take about 20 minutes. When would be convenient? *(record below)*

Consent and interview booking contact:

Dates phoned **Time phoned** **Outcome** (contacted / not contacted, did / did not consent)

_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____

(continue on another sheet if necessary)

Interview appointment date and time: _____

Date phoned **Time phoned** **Outcome** (interview completed, rebooked)

_____ _____
_____ _____
_____ _____

Subject no. | | | | | |

Consent Form 2: Next of kin who did not return the contact details form

Name(s) of case _____

Name(s) of next of kin _____

Relationship to case _____

Address _____

_____

Telephone number _____

Hello, may I please speak to (*name of next of kin*)?
I am Lianne Parkin, a doctor from the Otago Medical School. I am making follow up calls to people that I recently wrote to about our study of pulmonary embolism, and I am checking to see if you received my letter. Do you remember getting my letter?

If no: Offer to resend the letter *(check that we have the correct address).* **If they don't want us to resend letter:** I would like to be able to give you a little background information about our study before you make your final decision. **Then go on from **** *(if, following discussion, they agree to take part in the study repeat the offer to send the letter so that they have a copy for their records)*

If yes: As I said in the letter I sent you, **we are carrying out a major study on the causes of pulmonary embolism. Our aim is to identify factors that could help in preventing deaths from this condition in the future. We are interviewing the relatives of people who have died from pulmonary embolism about their life and health before they became unwell. If you agree to take part in the study, all the information you give us will be recorded without names and will be kept strictly confidential. Also if you do not want to answer particular questions that is fine. Do you have any questions about the study that you wish to ask? Would you be willing to help by answering some questions about your (*relative's*) life and health for our study?

Subject no. ☐☐☐ ☐

Consent: Obtained / Refused *1 = obtained 2 = refused* ☐

Signed: _____ **Date:** _____

If consent not given: Thank you very much for your time. Goodbye.

If consent given: I'd like to make a time for _____ to call you back for the telephone interview. It will take about 20 minutes. When would be convenient? *(record below)*

Consent and interview booking contact:

Dates phoned **Time phoned** **Outcome** (contacted / not contacted, did / did not consent)

_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____

(continue on another sheet if necessary)

Interview appointment date and time: _____

Date phoned **Time phoned** **Outcome** (interview completed, rebooked)

_____ _____
_____ _____
_____ _____

Subject no. | | | | | |

Consent Form 3: Controls who returned the contact details form

Name(s) _____

Address _____

_____

Telephone number _____

Hello, may I please speak to (*name of control*)?

I am Lianne Parkin, a doctor from the Otago Medical School. Thank you very much for returning the form that I sent you. You said that this would be a good time to speak to you, is it still alright? ***(If yes, continue. If no, ask: when would you like me to ring back? Record date and time on page 3)*** As I said in the letter I sent you, we are carrying out a major study on the causes of a serious condition that affects many New Zealanders every year. Our aim is to identify factors that could help in preventing deaths from this condition in the future. We are interviewing a large number of men and women all over New Zealand about their life and health. If you agree to take part in the study, all the information you give us will be recorded without your name and will be kept strictly confidential. Also if you do not want to answer particular questions that is fine. Do you have any questions about the study that you wish to ask? Would you be willing to help by answering some questions about your health for our study?

Consent: Obtained / Refused *1 = obtained 2 = refused* | |

Signed: _____ **Date:** _____

Subject no. | | | | | |

If consent not given: Thank you very much for your time. Before you go please may I ask you two quick questions that we are asking every one who is not taking part? Of course this entirely up to you.

Were you living in New Zealand on __/__/__ *(index date)* ?

(Prompt: if your home was in New Zealand but you were overseas on a holiday or a business trip on this date, you should answer yes to this question)

1 = yes 2 = no 3 = did not answer | |

Were you in New Zealand, or temporarily overseas on __/__/__ *(date of death of case)*?

1 = in NZ 2 = overseas 3 = did not answer | |

Thank you again for your time. Goodbye.

If consent given: In this study we want to interview people who were living in New Zealand on particular dates. Were you living in New Zealand on __/__/__ *(index date)* ?

(Prompt: if your home was in New Zealand but you were overseas on a holiday or a business trip on this date, you should answer yes to this question)

1 = yes 2 = no | |

If yes: I'd like to make a time for _____ to call you back for the telephone interview. It will take about 20 minutes. When would be convenient? *(record on next page)*

If no: Thank you very much for agreeing to be part of this study, but as you weren't living in New Zealand on this date we can't include you in the study. Thank you very much for your time. Goodbye.

Subject no. | | | | | |

Consent and interview booking contact:

Dates phoned **Time phoned** **Outcome** (contacted / not contacted, did / did not consent)

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

(continue on another sheet if necessary)

Interview appointment date and time: _____

Date phoned **Time phoned** **Outcome** (interview completed, rebooked)

_____ _____

_____ _____

_____ _____

Subject no. | | | | | |

Consent Form 4: Controls who did not return the contact details form

Name(s) _____

Address _____

_____

Telephone number _____

Hello, may I please speak to (*name of control*)?
I am Lianne Parkin, a doctor from the Otago Medical School. I am making follow up calls to people that I recently wrote to about a study we are carrying out, and I am checking to see if you received my letter. Do you remember getting my letter?

If no: Offer to resend the letter *(check that we have the correct address).* **If they don't want us to resend letter:** I would like to be able to give you a little background information about our study before you make your final decision. **Then go on from** ** *(if, following discussion, they agree to take part in the study repeat the offer to send the letter so that they have a copy for their records)*

If yes: As I said in the letter I sent you, ** we are carrying out a major study on the causes of a serious health condition that affects many New Zealanders every year. Our aim is to identify factors that could help in preventing deaths from this condition in the future. We are interviewing a large number of men and women all over New Zealand about their life and health. If you agree to take part in the study, all the information you give us will be recorded without your name and will be kept strictly confidential. Also if you do not want to answer particular questions that is fine. Do you have any questions about the study that you wish to ask? Would you be willing to help by answering some questions about your health for our study?

Subject no. ☐☐☐ ☐

Consent: Obtained / Refused *1 = obtained 2 = refused* ☐

Date: _____ ☐☐ ☐☐ ☐☐

Signed: _____ ☐

If consent not given: Thank you very much for your time. Before you go please may I ask you two quick questions that we are asking every one who is not taking part? Of course this entirely up to you.

Were you living in New Zealand on __/__/__ *(index date)* ?

(Prompt: if your home was in New Zealand but you were overseas on a holiday or a business trip on this date, you should answer yes to this question)

1 = yes 2 = no 3 = did not answer ☐

Were you in New Zealand, or temporarily overseas on __/__/__ *(date of death of case)*?

1 = in NZ 2 = overseas 3 = did not answer ☐

Thank you again for your time. Goodbye.

If consent given: In this study we want to interview people who were living in New Zealand on particular dates. Were you living in New Zealand on __/__/__ *(index date)* ?

(Prompt: if your home was in New Zealand but you were overseas on a holiday or a business trip on this date, you should answer yes to this question)

1 = yes 2 = no ☐

Subject no. | | | | | |

If yes: I'd like to make a time for _____ to call you back for the telephone interview. It will take about 20 minutes. When would be convenient? *(record below)*

If no: Thank you very much for agreeing to be part of this study, but as you weren't living in New Zealand on this date we can't include you in the study. Thank you very much for your time. Goodbye.

Consent and interview booking contact:

Dates phoned	**Time phoned**	**Outcome** (contacted / not contacted, did / did not consent)
_____	_____	
_____	_____	
_____	_____	
_____	_____	
_____	_____	
_____	_____	
_____	_____	
_____	_____	
_____	_____	
_____	_____	

(continue on another sheet if necessary)

Interview appointment date and time: _____

Date phoned	**Time phoned**	**Outcome** (interview completed, rebooked)
_____	_____	
_____	_____	
_____	_____	

APPENDIX E: INTERVIEWER-ADMINISTERED QUESTIONNAIRE

Note:

1. On the following pages, the questionnaire sections are ordered according to the sequence in which they appeared on the computer screen during the telephone interview (that is, 1, 2, 3, 4a, 9a, 10, 5, 6, 7, and 8). The reason why the sections do not follow a strictly numerical sequence is that at the time the Abbey CATI software® was used, it was not possible to change the numbering of a section after it had been created.

2. When the computerised version of the questionnaire was developed, a "loop" was incorporated so that it was possible to ask questions regarding up to 15 international journeys by air and up to 15 domestic air journeys (within countries other than New Zealand). On the following pages, however, only one set of questions is shown for each type of journey.

Fatal pulmonary embolism and long-distance air travel study

Medical history

Section 1

Q00a Hello, may I please speak to <> <>? I am <> from the Otago Medical School. Thank you very much for agreeing to participate in our study of health problems. Is it still convenient to do the interview now? **Q00a**

Before we begin, I'd like to emphasize that all the information you give me will be confidential and will be recorded without your name. You don't need to answer all the questions, and you may stop the interview at any time if you wish. I need to type your answers, so you might hear me typing during the interview.

Do you have the calendar that we sent in front of you?

IF YES: That's good. You'll also need a pen or pencil. Have you got one handy?

(IF NO: ask them to go and get it. If they have lost it: fax them the calendar if possible, otherwise arrange to post another copy and reschedule the interview)

During this interview I'm going to ask you questions about what <>your<><>your <>'s<> health was like before a particular date. That date is the <>. So before I ask you any more questions, I'd like you circle this date on your calendar. I'd also like you to circle two other dates. They are the <> and the <>.

Response type: Statement

Default next: 1 -00b

(Added 10/03/2003 04:43:27 PM by lparkin Modified 27/05/2003 08:55:58 PM by lianne parkin)

Q00b <>To help you remember what your health was like before the <> it might be useful to think about where you were living on that date and how old you were. **Q00b**

You could also think about particular events that happened around that time. For some people this might be a new job, a holiday, or the birth of a child.

I'll give you a little bit of time to think about this now. You might find that it's helpful to write some things on the calendar.

I don't need you to tell me about any of these things - it's just to help jog your memory about the time before the <>. Let me know when you're ready to carry on with the interview.<>

I'd like to start the interview by asking a few SHORT questions about what <>your<> <>your <>'s<> health was like before the <>.

For most of these questions a 'yes' or 'no' answer is all that I need. <-IIF(Ireference.ucontrol and lower(reference.usamedate)<>"yes",[It might be helpful to look at the calendar as you answer these questions, just to remind yourself that I'm ONLY asking about your <>'s health from the time <>s<>he was born up until the <>.],")->

<>I realise that you probably won't know every detail of your <>'s medical history. Please just answer these questions as best as you can.<>

Response type: Statement

Default next: 1 -01

(Added 14/03/2003 02:32:41 PM by lparkin Modified 28/05/2003 12:54:07 PM by lianne parkin)

Q01 So, before the <>, <>were you <><>was your <><> EVER treated for any of the following conditions? **Q01**

Angina?

Response type: Single select from

Yes
No
Don't know

Default next: 1 -02

(Added 07/03/2003 01:50:39 PM by lparkin Modified 14/05/2003 05:46:53 PM by lianne parkin)

Q02 A heart attack? **Q02**

Response type: Single select from

Yes
No
Don't know

Default next: 1 -03

(Added 14/05/2003 05:11:48 PM by lianne parkin Modified / / : : AM by)

Q03 A stroke? **Q03**

Response type: Single select from

Yes
No
Don't know

Default next: 1 -04

(Added 14/05/2003 05:12:12 PM by lianne parkin Modified / / : : AM by)

Q04 High blood pressure <><>at a time when you WEREN'T PREGNANT<>?<><><>at a time when she WASN'T PREGNANT<>?<> **Q04**

Response type: Single select from

Yes
No
Don't know

Default next: 1 -05

(Added 14/05/2003 05:12:44 PM by lianne parkin Modified / / : : AM by)

Q05 Systemic lupus erythematosis or SLE? **Q05**

(PROMPT IF NECESSARY: SLE is a chronic condition in which people often develop a rash over their cheekbones, as well as problems with their kidneys, spleen, lungs, heart, brain, and joints.)

Response type: Single select from

Yes
No
Don't know

Default next: 1 -06

(Added 14/05/2003 05:13:26 PM by lianne parkin Modified 14/05/2003 05:47:06 PM by lianne parkin)

Q06 Crohn's disease or ulcerative colitis? **Q06**

(PROMPT IF NECESSARY: People with these diseases have inflammation of the intestine and serious diarrhoea)

Response type: Single select from

Yes
No
Don't know

Default next: 1 -07a

(Added 14/05/2003 05:13:51 PM by lianne parkin Modified 16/05/2003 02:32:39 PM by lianne parkin)

Q07a Now I just want to check that I've recorded your answers correctly. **Q07a**

I have recorded that before the <>, <>you

WERE<><>your <> WAS<> treated for:

<-iif(Qdata1.q01=1,'Angina'+CHR(13),'')-><-iif(Qdata1.q02=1,'A heart attack'+CHR(13),'')-><-iif(Qdata1.q03=1,'A stroke'+CHR(13),'')-><-iif(Qdata1.q04=1,'High blood pressure'+CHR(13),'')-><-iif(Qdata1.q05=1,'Systemic lupus erythematosis'+CHR(13),'')-><-iif(Qdata1.q06=1,"Crohn's disease or ulcerative colitis",'')->

Is that correct? (make corrections as necessary)

Response type: Statement

Default next: 1 -07b

(Added 14/05/2003 05:15:10 PM by lianne parkin Modified 19/05/2003 11:21:50 AM by lianne parkin)

Q07b And <>you WEREN'T<><>your <>WASN'T<> treated for: **Q07b**

<-iif(Qdata1.q01=2,'Angina'+CHR(13),'')-><-iif(Qdata1.q02=2,'A heart attack'+CHR(13),'')-><-iif(Qdata1.q03=2,'A stroke'+CHR(13),'')-><-iif(Qdata1.q04=2,'High blood pressure'+CHR(13),'')-><-iif(Qdata1.q05=2,'Systemic lupus erythematosis'+CHR(13),'')-><-iif(Qdata1.q06=2,"Crohn's disease or ulcerative colitis",'')->

Is that correct? (make corrections as necessary)

Response type: Statement

Default next: 1 -07c

(Added 14/05/2003 05:36:29 PM by lianne parkin Modified 16/05/2003 04:21:50 PM by lianne parkin)

Q07c And you DON'T KNOW whether <>you were<><>your <> was<> treated for: **Q07c**

<-iif(Qdata1.q01=3,'Angina'+CHR(13),'')-><-iif(Qdata1.q02=3,'A heart attack'+CHR(13),'')-><-iif(Qdata1.q03=3,'A stroke'+CHR(13),'')-><-iif(Qdata1.q04=3,'High blood pressure'+CHR(13),'')-><-iif(Qdata1.q05=3,'Systemic lupus erythematosis'+CHR(13),'')-><-iif(Qdata1.q06=3,"Crohn's disease or ulcerative colitis",'')->

Is that correct? (correct answers as necessary)

Response type: Statement

Default next: 1 -08a

(Added 14/05/2003 05:44:54 PM by lianne parkin Modified 16/05/2003 04:23:19 PM by lianne parkin)

Q08a <>Were you<><>Was your <><> EVER treated for any other heart problems? **Q08a**

Response type: Single select from

Yes
No
Don't know

Response logic:

1 08b

Default next: 1 -09a

(Added 09/05/2003 04:12:28 PM by lianne parkin Modified 14/05/2003 04:25:04 PM by lianne parkin)

Q08b What was the problem(s) <>you were<><><><>s<>he was<> treated for? **Q08b**

Response type: Single line text

200

Response logic:

Default next: 1 -08c

(Added 07/03/2003 04:13:51 PM by lparkin Modified 14/05/2003 04:25:59 PM by lianne parkin)

Q08c What is (are) the ICD-9 code(s)? **Q08c**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:1 08d
Response type: Numeric
999.9
Default next: 1 -08d
(Added 11/03/2003 05:17:53 PM by lparkin Modified 14/05/2003 04:59:40 PM by lianne parkin)

Q08d Before the <> **Q08d**

Response type: Statement
Default next: 1 -09a
(Added 20/03/2003 05:07:22 PM by lparkin Modified 14/05/2003 05:03:13 PM by lianne parkin)

Q09a <>Were you<><>Was your <><> EVER treated for diabetes? **Q09a**

Response type: Single select from
Yes
No
Don't know

Response logic:
1 09b

Default next: 1 -10a
(Added 07/03/2003 04:18:51 PM by lparkin Modified 14/05/2003 04:56:49 PM by lianne parkin)

Q09b What type of diabetes did <>you<><><><>s<>he<> have? **Q09b**

PROMPT IF NECESSARY: <>Were you<><>Was <>s<>he<> treated with insulin injections, with tablets, or with a particular diet?

Response type: Single select from
Insulin dependent
Non-insulin dependent
Gestational diabetes only
Unknown

Default next: 1 -09c
(Added 07/03/2003 04:20:47 PM by lparkin Modified 14/05/2003 04:50:38 PM by lianne parkin)

Q09c Before the <> **Q09c**

Response type: Statement
Default next: 1 -10a
(Added 20/03/2003 05:10:27 PM by lparkin Modified 14/05/2003 04:50:55 PM by lianne parkin)

Q10a <>Were you<><>Was your <><> EVER treated for kidney problems? **Q10a**

Response type: Single select from
Yes
No
Don't know

Response logic:
1 10b

Default next: 1 -11a
(Added 07/03/2003 04:34:16 PM by lparkin Modified 14/05/2003 04:51:13 PM by lianne parkin)

Q10b What was the problem(s) <>you were<><><><>s<>he was<> treated for? **Q10b**

IF "KIDNEY INFECTION" STATED, ASK:
<>Were you <><>Was <>s<>he <> treated with antibiotics? How many days <>were you <><>was <>s<>he<> treated for? <>Were you <><>Was <>s<>he <> admitted to hospital? <>Were you <><>Was <>s<>he <> given intravenous (via a drip) antibiotics?

IF "KIDNEY STONE" STATED, ASK: How was the stone diagnosed? Did <>you<><><><>s<>he <> have an XRay or ultrasound? What treatment <>were you<><>was <>s<>he<> given?

Response type: Single line text

200

Default next: 1 -10c

(Added 07/03/2003 04:36:17 PM by lparkin Modified 19/05/2003 11:29:39 AM by lianne parkin)

Q10c What is (are) the ICD-9 code(s)?) **Q10c**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:1 10d

Response type: Numeric

999.9

Default next: 1 -10d

(Added 11/03/2003 05:23:23 PM by lparkin Modified 14/05/2003 05:00:38 PM by lianne parkin)

Q10d Before the <> **Q10d**

Response type: Statement

Default next: 1 -11a

(Added 20/03/2003 05:52:54 PM by lparkin Modified 14/05/2003 04:52:01 PM by lianne parkin)

Q11a <>Were you<> <>Was your <><> EVER treated for liver problems? **Q11a**

Response type: Single select from

Yes
No
Don't know

Response logic:

1 11b

Default next: 1 -12a

(Added 07/03/2003 04:37:30 PM by lparkin Modified 14/05/2003 04:52:19 PM by lianne parkin)

Q11b What was the problem(s) <>you were<><><><>s<>he was<> treated for? **Q11b**

Response type: Single line text

200

Default next: 1 -11c

(Added 07/03/2003 04:38:04 PM by lparkin Modified 14/05/2003 04:52:34 PM by lianne parkin)

Q11c What is (are) the ICD-9 code(s)? **Q11c**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:1 11d

Response type: Numeric

999.9

Default next: 1 -11d

(Added 11/03/2003 05:26:49 PM by lparkin Modified 14/05/2003 05:01:19 PM by lianne parkin)

Q11d Before the <> **Q11d**

Response type: Statement

Default next: 1 -12a

(Added 20/03/2003 05:59:07 PM by lparkin Modified 14/05/2003 04:53:07 PM by lianne parkin)

Q12a <>Were you<><>Was your <><> EVER treated for cancer? **Q12a**

Response type: Single select from

Yes
No
Don't know

Response logic:
1 12b

Default next: 1 -13a

(Added 07/03/2003 04:39:15 PM by lparkin Modified 14/05/2003 04:53:23 PM by lianne parkin)

Q12b What type(s) of cancer did <>you <><><>s<>he<> have? **Q12b**

NB. IF BONE, BRAIN, OR LIVER CANCER STATED, ASK: Where did the cancer start?

IF SKIN CANCER STATED, ASK: Was it a melanoma skin cancer?

IF CERVICAL CANCER STATED, ASK: What treatment <>were you <><>was <>she<><> given?

Response type: Single line text

200

Default next: 1 -12c

(Added 07/03/2003 04:39:42 PM by lparkin Modified 14/05/2003 08:30:29 PM by lianne parkin)

Q12c When was the cancer first diagnosed? **Q12c**

Response type: Single line text

Default next: 1 -12d

(Added 07/03/2003 04:40:04 PM by lparkin Modified 14/05/2003 04:53:52 PM by lianne parkin)

Q12d What is (are) the ICD-9 code(s)? **Q12d**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:1 12e

Response type: Numeric

999.9

Default next: 1 -12e

(Added 11/03/2003 05:31:02 PM by lparkin Modified 14/05/2003 05:01:50 PM by lianne parkin)

Q12e Before the <> **Q12e**

Response type: Statement

Default next: 1 -13a

(Added 20/03/2003 06:02:59 PM by lparkin Modified 14/05/2003 04:54:20 PM by lianne parkin)

Q13a Did <>you <><>your <><> EVER have varicose veins? **Q13a**

Response type: Single select from

Yes
No
Don't know

Response logic:
1 13b

Default next: 1 -14a

(Added 01/02/2003 12:00:00 AM by cblakey Modified 14/05/2003 04:54:39 PM by lianne parkin)

Q13b <>Did you ever have treatment for your varicose veins?<><>Did your <> ever have treatment for <>her<><>his<> varicose veins?<> (surgery, sclerosing, or other intervention) **Q13b**

Response type: Single select from

Yes
No
Don't know

Default next: 1 -13c

(Added 01/02/2003 12:00:00 AM by cblakey Modified 14/05/2003 04:54:54 PM by lianne parkin)

Q13c Before the <> **Q13c**

Response type: Statement

Default next: 1 -14a

(Added 20/03/2003 06:06:50 PM by lparkin Modified 14/05/2003 04:57:41 PM by lianne parkin)

Q14a Did <>you<><>your <><> EVER have a blood clot in the veins of <>your<><><>her<><>his<</Umale >><> legs? **Q14a**

PROMPT IF NECESSARY: Blood clots can occur in the veins on the SURFACE of the legs AND in the DEEP veins. The medical name for blood clots in the veins on the surface of the legs is superficial venous thrombosis or thrombophlebitis; and the medical name for blood clots in the deep veins of the legs or pelvis is deep vein thrombosis (or DVT for short).

Response type: Single select from

Yes
No
Don't know

Response logic:

1 14b

Default next: 1 -15a

(Added 07/03/2003 05:45:06 PM by lparkin Modified 14/05/2003 04:55:20 PM by lianne parkin)

Q14b Was the blood clot in the veins on the SURFACE of your <><>'s<> leg, OR in the DEEP VEINS of <>your<><><>her<><>his<</Umale>><> leg? **Q14b**

PROMPT IF NECESSARY: The medical names for blood clots in the veins on the surface of the legs are superficial venous thrombosis or thrombophlebitis; and the medical name for blood clots in the deep veins of the legs or pelvis is deep vein thrombosis, or DVT or short.

Response type: Single select from

Superficial only
Deep only
Both, concurrently
Both, at different times
Don't know

Post-logic: Qdata1.q14b=1 or Qdata1.q14b=3 or Qdata1.q14b=4 GOTO:1 14c
Qdata1.q14b=2 GOTO:1 14h
Qdata1.q14b=5 GOTO:1 14m

Default next: 1 -15a

(Added 07/03/2003 05:51:04 PM by lparkin Modified 14/05/2003 05:05:27 PM by lianne parkin)

Q14c I'd like to ask you some more questions about the clot in the veins on the SURFACE of your<> <>'s<> leg. **Q14c**

When was the (first episode if > 1) clot diagnosed?

Response type: Single line text

200

Default next: 1 -14d

(Added 07/03/2003 05:53:45 PM by lparkin Modified 14/05/2003 04:56:05 PM by lianne parkin)

Q14d <>Were you<><>Was your <><> treated for the (first episode if > 1) clot? **Q14d**

Response type: Single select from

Yes
No
Don't know

Response logic:

1 14e

Default next: 1 -14f

(Added 07/03/2003 05:55:58 PM by lparkin Modified 14/05/2003 04:56:25 PM by lianne parkin)

Q14e What treatment <>were you <><>was <>s<>he<> given? **Q14e**

READ OUT IF NECESSARY AND SELECT AS MANY AS APPLY (scroll down):
1. A drug to thin the blood that was given through an intravenous drip or injected under the skin (heparin or low molecular weight heparin)
2. Pills to thin the blood such as warfarin or coumarin (usually given for at least 3 months)
3. Aspirin or other pills (other than warfarin / coumarin) that help to thin the blood
4. Anti-inflammatory pills
5. Antibiotic pills
6. Ointments
7. Bed rest
8. Other

Response type: Multichoice from

Heparin / LMWH
Warfarin / coumarin
Aspirin or other pills
Anti-inflammatories
Antibiotics
Ointments
Bed rest
Other

Default next: 1 -14f

(Added 07/03/2003 06:01:39 PM by lparkin Modified 14/05/2003 04:49:01 PM by lianne parkin)

Q14f Did the (first episode if > 1) clot occur at any particular time, for example: **Q14f**

<><>During pregnancy?
After giving birth?<><>
<><>During pregnancy?
After giving birth?<><>
After an operation?
After an injury?
During an illness?

Response type: Single select from

Yes
No
Don't know

Response logic:

1 14g

Default next: 1 -14h

(Added 07/03/2003 06:03:09 PM by lparkin Modified 14/05/2003 04:48:39 PM by lianne parkin)

Q14g What were the circumstances? **Q14g**

Response type: Multichoice from

Pregnancy / puerperium
Postoperative
Injury
Illness
Other

Default next: 1 -14h

(Added 07/03/2003 06:05:16 PM by lparkin Modified 14/05/2003 04:48:11 PM by lianne parkin)

Q14h I'd like to ask you some more questions about the clot in the DEEP veins of your <><>'s<> leg. The medical name for this condition is deep vein thrombosis. So, when was the (first episode if > 1) deep vein thrombosis diagnosed? **Q14h**

Pre-logic: Qdata1.q14b=1 GOTO:1 14r
Response type: Single line text
Default next: 1 -14i

(Added 07/03/2003 06:05:59 PM by lparkin Modified 14/05/2003 05:06:09 PM by lianne parkin)

Q14i <>Were you<><>Was your <><> given treatment for the (first episode if > 1) deep vein thrombosis? **Q14i**

Response type: Single select from

Yes
No
Don't know

Response logic:
1 14j

Default next: 1 -14k

(Added 07/03/2003 06:10:29 PM by lparkin Modified 14/05/2003 04:47:35 PM by lianne parkin)

Q14j What treatment <>were you<><>was <>s<>he<> given? **Q14j**

READ OUT IF NECESSARY AND SELECT AS MANY AS APPLY (scroll down):
1. A drug to thin the blood that was given through an intravenous drip or injected under the skin (heparin or low molecular weight heparin)
2. Pills to thin the blood such as warfarin or coumarin
3. Aspirin or other pills that help to thin the blood
4. Anti-inflammatory pills
5. Antibiotic pills
6. Ointments
7. Bed rest
8. Other

Response type: Multichoice from

Heparin / LMWH
Warfarin / coumarin
Aspirin or other pills
Anti-inflammatories
Antibiotics
Ointments
Bed rest
Other

Default next: 1 -14k

(Added 07/03/2003 06:11:13 PM by lparkin Modified 14/05/2003 04:47:20 PM by lianne parkin)

Q14k Did the (first episode if > 1) deep vein thrombosis occur at any particular time, for example: **Q14k**

<><>During pregnancy?
After giving birth?<><>
<><>During pregnancy?
After giving birth?<><>
After an operation?
After an injury?
During an illness?

Response type: Single select from

Yes
No
Don't know

Response logic:
1 14l

Default next: 1 -14r

(Added 07/03/2003 06:13:05 PM by lparkin Modified 14/05/2003 04:47:09 PM by lianne parkin)

Q14l What were the circumstances? **Q14l**

Response type: Multichoice from

Pregnancy / puerperium
Postoperative
Injury
Illness
Other

Default next: 1 -14r

(Added 07/03/2003 06:14:47 PM by lparkin Modified 14/05/2003 04:46:53 PM by lianne parkin)

Q14m I'd like to ask you some more questions about the clot. When was it (first episode if > 1) diagnosed? **Q14m**

Pre-logic: Qdata1.q14b<>5 GOTO:1 15a
Response type: Single line text
Default next: 1 -14n

(Added 11/03/2003 06:06:26 PM by lparkin Modified 14/05/2003 08:23:42 PM by lianne parkin)

Q14n <>Were you<><>Was your <> <> given treatment for the (first episode if > 1) clot? **Q14n**

Response type: Single select from

Yes
No
Don't know

Response logic:
1 14o

Default next: 1 -14p

(Added 11/03/2003 06:08:04 PM by lparkin Modified 14/05/2003 04:46:28 PM by lianne parkin)

Q14o What treatment <>were you<><>was <>s<>he<> given? **Q14o**

READ OUT IF NECESSARY, AND SELECT AS MANY AS APPLY (scroll down):
1. A drug to thin the blood that was given through an intravenous drip or injected under the skin (heparin or low molecular weight heparin)
2. Pills to thin the blood such as warfarin or coumarin
3. Aspirin or other pills that help to thin the blood
4. Anti-inflammatory pills
5. Antibiotic pills
6. Ointments
7. Bed rest
8. Other

Response type: Multichoice from

Heparin / LMWH
Warfarin / coumarin
Aspirin or other pills
Anti-inflammatories
Antibiotics
Ointments
Bed rest
Other

Default next: 1 -14p

(Added 11/03/2003 06:09:22 PM by lparkin Modified 14/05/2003 04:35:04 PM by lianne parkin)

Q14p Did the (first episode if > 1) clot occur at any particular time, for example: **Q14p**
<><>During pregnancy?
After giving birth?<><>
<><>During pregnancy?
After giving birth?<><>
After an operation?
After an injury?
During an illness?

Response type: Single select from

Yes
No
Don't know

Response logic:

1 14q

Default next: 1 -14r

(Added 11/03/2003 06:11:44 PM by lparkin Modified 14/05/2003 04:34:47 PM by lianne parkin)

Q14q What were the circumstances? **Q14q**

Response type: Multichoice from

Pregnancy / puerperium
Postoperative
Injury
Illness
Other

Default next: 1 -14r

(Added 11/03/2003 06:15:24 PM by lparkin Modified 14/05/2003 04:34:29 PM by lianne parkin)

Q14r Before the <> **Q14r**

Response type: Statement

Default next: 1 -15a

(Added 20/03/2003 06:08:21 PM by lparkin Modified 14/05/2003 04:34:14 PM by lianne parkin)

Q15a <>Were you <><>Was your <><> EVER treated for pulmonary embolism? **Q15a**

PROMPT IF REQUIRED This is a condition where blood clots, which have formed in the veins of the legs or pelvis, break off and travel up to the arteries of the lungs.

Response type: Single select from

Yes
No
Don't know

Response logic:

1 15b

Default next: 1 -16a

(Added 01/02/2003 12:00:00 AM by cblakey Modified 14/05/2003 04:34:00 PM by lianne parkin)

Q15b When was the (first episode if > 1) pulmonary embolism diagnosed? **Q15b**

Response type: Single line text

Default next: 1 -15c

(Added 01/02/2003 12:00:00 AM by cblakey Modified 14/05/2003 04:33:43 PM by lianne parkin)

Q15c <>Were you<><>Was your <><> treated with medication to thin the blood (heparin, warfarin, coumarin)? **Q15c**

Response type: Single select from

Yes
No
Don't know

Default next: 1 -15d

(Added 07/03/2003 06:20:54 PM by lparkin Modified 14/05/2003 04:29:03 PM by lianne parkin)

Q15d Did the (first episode if > 1) pulmonary embolism occur at any particular time, for example: **Q15d**

<><>During pregnancy?
After giving birth?<><>
<><>During pregnancy?
After giving birth?<><>
After an operation?
After an injury?
During an illness?

Response type: Single select from

Yes
No
Don't know

Response logic:

1 15e

Default next: 1 -15f

(Added 07/03/2003 06:22:12 PM by lparkin Modified 14/05/2003 04:28:51 PM by lianne parkin)

Q15e What were the circumstances? **Q15e**

Response type: Multichoice from

Pregnancy / puerperium
Postoperative
Injury
Illness
Other

Default next: 1 -15f

(Added 11/03/2003 06:25:21 PM by lparkin Modified 14/05/2003 04:28:34 PM by lianne parkin)

Q15f Before the <> **Q15f**

Response type: Statement

Default next: 1 -16a

(Added 20/03/2003 06:11:36 PM by lparkin Modified 14/05/2003 04:28:23 PM by lianne parkin)

Q16a <>Were you EVER told that you had a blood disorder which increased the chances of developing deep vein thrombosis or pulmonary embolism?<><>Was your <> EVER told that <>s<>he had a blood disorder which increased the chances of developing deep vein thrombosis or pulmonary embolism?<> **Q16a**

PROMPT IF REQUIRED Deep vein thrombosis is the condition where blood clots form in the deep veins of the legs or pelvis. And pulmonary embolism is the condition where these blood clots break off and travel up to the arteries of the lungs.

Response type: Single select from

Yes
No
Don't know

Response logic:

1 16b

Default next: 2 -00

(Added 01/02/2003 12:00:00 AM by cblakey Modified 27/05/2003 03:48:35 PM by lianne parkin)

Q16b I am going to read out the names of some blood disorders. I would like you to tell me if <>you were<><>your <> was <>diagnosed with any of these disorders: **Q16b**

(Read out name of each disorder. Select as many as apply, otherwise record unknown)

Response type: Multichoice from

Factor 5 Leiden
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Dysfibrinogenaemia
Plasminogen deficiency
Prothrombin variant
High factor 8
Increased platelets
Homocysteinaemia
Antiphospholipid syndrome
Anticardiolipin antibodies
Lupus anticoagulant
Unknown

Default next: 2 -00

(Added 01/02/2003 12:00:00 AM by cblakey Modified 14/05/2003 04:27:57 PM by lianne parkin)

Q00 Now I would like to ask a few questions about pregnancy and any female hormones <>you<><>your <><> might have taken before the <> **Q00**

Pre-logic: (!Reference.ucontrol and Reference.umale) or (Reference.ucontrol and Reference.male) GOTO:300

Response type: Statement

Default next: 2 -01a

(Added 12/03/2003 09:43:05 AM by lparkin Modified 08/05/2003 03:09:08 PM by lianne parkin)

Q01a <>Did you<><>Did your <><> give birth to any children before the <>? **Q01a**

Response type: Single select from

Yes
No
Don't know

Response logic:

2 01b

Default next: 2 -02

(Added 10/03/2003 11:47:02 AM by lparkin Modified 28/03/2003 04:20:51 PM by lparkin)

Q01b How many children did <>you<><>she<> have before this date?
(record "-2" if don't know) **Q01b**

Response type: Numeric

99

Default next: 2 -01c

(Added 10/03/2003 11:48:52 AM by lparkin Modified 31/03/2003 05:46:42 PM by lparkin)

Q01c Before the <> did <>you<><>your <><> ever have high blood pressure DURING PREGNANCY that required treatment with medication or with bed rest in hospital? **Q01c**

Response type: Single select from

Yes
No
Don't know

Default next: 2 -02

(Added 10/03/2003 11:53:29 AM by lparkin Modified 28/03/2003 04:38:23 PM by lparkin)

Q02 Before the <> did <>you<><>your <><> EVER use the oral contraceptive pill (the pill)? **Q02**

Response type: Single select from

Yes
No
Don't know

Default next: 2 -03

(Added 10/03/2003 11:53:53 AM by lparkin Modified 31/03/2003 05:47:13 PM by lparkin)

Q03 Before the <> did <>you<><>your <><> EVER take hormone replacement therapy or HRT? **Q03**

PROMPT IF NECESSARY: By hormone replacement therapy I mean the female hormone pills, skin patches, or implants that some women use around the time of the menopause or the change of life.

Response type: Single select from

Yes
No
Don't know

Default next: 3 -00

(Added 10/03/2003 11:58:09 AM by lparkin Modified 16/04/2003 11:49:28 AM by lianne parkin)

VTE risk factors in the three months before the index date

Q00 Now I am going to ask you some questions about particular events during the three months before the <>. **Q00**

If you look at your calendar, you'll see that I'm talking about the period between the <> and the <>.

So:

Response type: Statement

Default next: 3 -01a

(Added 12/03/2003 09:43:52 AM by lparkin Modified 10/05/2003 04:59:35 PM by lianne parkin)

Q01a During those three months <>were you<><>was your <><> treated for a broken bone? **Q01a**

(If limb fracture, record whether left or right limb)

Response type: Single select from

Yes
No
Don't know

Response logic:

3 01b

Default next: 3 -02a

(Added 10/03/2003 12:04:31 PM by lparkin Modified 13/05/2003 09:42:33 PM by lianne parkin)

Q01b Which bone(s) did <>you<><><>s<>he<> break? **Q01b**

Response type: Single line text

200

Default next: 3 -01c

(Added 10/03/2003 12:06:45 PM by lparkin Modified 11/05/2003 06:33:00 PM by lianne parkin)

Q01c When did <>you<><><>s<>he<> break it? (record date / don't know) **Q01c**

Response type: Single line text

200

Default next: 3 -01d

(Added 10/03/2003 12:07:58 PM by lparkin Modified 31/03/2003 05:48:30 PM by lparkin)

Q01d How was it treated? **Q01d**

Response type: Single line text

200

Default next: 3 -01e

(Added 10/03/2003 12:10:51 PM by lparkin Modified 13/04/2003 03:09:00 PM by lparkin)

Q01e That's the end of the questions about your <><>'s<> broken bone(s). **Q01e**

Now I'm going to ask you some more questions about OTHER events in the three months between the <> and the <>.

Response type: Statement

Default next: 3 -02a

(Added 13/04/2003 03:08:52 PM by lparkin Modified 12/05/2003 01:23:19 PM by lianne parkin)

Q02a During those three months <>were you<><>was your <><> admitted to hospital because of an injury? **Q02a**

Response type: Single select from

Yes
No
Don't know

Response logic:
3 02b

Default next: 3 -03a

(Added 10/03/2003 12:12:37 PM by lparkin Modified 13/04/2003 03:16:38 PM by lparkin)

Q02b What was the injury? **Q02b**

(If injured limb, record whether left or right limb)

Response type: Single line text
200

Default next: 3 -02c

(Added 10/03/2003 12:13:02 PM by lparkin Modified 13/05/2003 09:42:45 PM by lianne parkin)

Q02c When <>were you<><>was <>s<>he<> injured? **Q02c**
(record date / don't know)

Response type: Single line text
200

Default next: 3 -02d

(Added 10/03/2003 12:14:13 PM by lparkin Modified 31/03/2003 05:49:04 PM by lparkin)

Q02d What treatment(s) did <>you<><><>s<>he<> have? **Q02d**

Response type: Single line text
200

Default next: 3 -02e

(Added 10/03/2003 12:15:07 PM by lparkin Modified 14/03/2003 05:42:57 PM by lparkin)

Q02e Which hospital(s) <>were you<><>was <>s<>he<> admitted to? **Q02e**

Response type: Single line text
200

Default next: 3 -02f

(Added 10/03/2003 01:52:03 PM by lparkin Modified 14/03/2003 05:43:17 PM by lparkin)

Q02f How many days <>were you<><>was <>s<>he<> in hospital? **Q02f**
(record number of days / don't know)

Response type: Single line text
200

Default next: 3 -02g

(Added 10/03/2003 12:17:36 PM by lparkin Modified 13/04/2003 03:16:04 PM by lparkin)

Q02g That's the end of the questions about <>your<><>your <>'s<> admission to hospital with the injury. **Q02g**

Now I'm going to ask you some more questions about OTHER events in the three months between the <> and the <>.

Response type: Statement

Default next: 3 -03a

(Added 13/04/2003 03:15:55 PM by lparkin Modified 12/05/2003 01:23:10 PM by lianne parkin)

Q03a During those three months did <>you<><>your <><> have any operations? **Q03a**

Response type: Single select from

Yes
No
Don't know

Response logic:
3 03b

Default next: 3 -04a

(Added 10/03/2003 12:18:54 PM by lparkin Modified 13/04/2003 03:17:09 PM by lparkin)

Q03b What was the operation(s)? **Q03b**

(If limb surgery, record whether left or right limb)

Response type: Single line text
200

Default next: 3 -03c

(Added 10/03/2003 12:19:27 PM by lparkin Modified 13/05/2003 09:42:54 PM by lianne parkin)

Q03c On what date(s) did <>you<><><>s<>he<> have the operation(s)? **Q03c**
(record date / don't know)

Response type: Single line text
200

Default next: 3 -03d

(Added 10/03/2003 12:21:32 PM by lparkin Modified 31/03/2003 05:51:06 PM by lparkin)

Q03d In which hospital(s) did <>you<><><>s<>he<> have the operation(s)? **Q03d**

Response type: Single line text
200

Default next: 3 -03e

(Added 10/03/2003 12:22:52 PM by lparkin Modified 13/03/2003 10:09:18 AM by lparkin)

Q03e How many days<> were you<><> was <>s<>he<> in hospital? **Q03e**
(record number of days / don't know)

Response type: Single line text
200

Default next: 3 -03f

(Added 10/03/2003 12:24:40 PM by lparkin Modified 13/04/2003 03:18:29 PM by lparkin)

Q03f That's the end of the questions about your <><>'s<> operation(s). **Q03f**

Now I'm going to ask you some more questions about OTHER events in the three months between the <> and the <>.

Response type: Statement

Default next: 3 -04a

(Added 13/04/2003 03:18:21 PM by lparkin Modified 12/05/2003 01:23:32 PM by lianne parkin)

Q04a During those three months <>were you<><>was your <><> admitted to hospital for any other reason? **Q04a**

Response type: Single select from

Yes
No
Don't know

Response logic:
3 04b

Default next: 3 -05a

(Added 10/03/2003 01:55:29 PM by lparkin Modified 13/04/2003 03:17:23 PM by lparkin)

Q04b What was the reason <>you were <><><>s<>he was<> admitted? **Q04b**

Response type: Single line text
200
Default next: 3 -04c
(Added 10/03/2003 02:01:17 PM by lparkin Modified 13/03/2003 10:11:26 AM by lparkin)

Q04c Which hospital(s) <>were you<><>was <>s<>he<> admitted to? **Q04c**

Response type: Single line text
200
Default next: 3 -04d
(Added 10/03/2003 02:02:50 PM by lparkin Modified 11/05/2003 03:27:44 PM by lianne parkin)

Q04d On what date(s) <>were you<><>was <>s<>he<> admitted to hospital? **Q04d**
(record date / don't know)

Response type: Single line text
200
Default next: 3 -04e
(Added 10/03/2003 02:04:33 PM by lparkin Modified 31/03/2003 05:51:49 PM by lparkin)

Q04e How many days <>were you<><>was <>s<>he<> in hospital? **Q04e**
(record number of days / don't know)

Response type: Single line text
200
Default next: 3 -04f
(Added 10/03/2003 02:05:25 PM by lparkin Modified 16/04/2003 11:51:44 AM by lianne parkin)

Q04f That's the end of the questions about your <><>'s<> hospital admission. **Q04f**

Now I'm going to ask you some more questions about OTHER events in the three months between the <> and the <>.

Response type: Statement
Default next: 3 -05a
(Added 13/04/2003 03:20:02 PM by lparkin Modified 12/05/2003 01:23:45 PM by lianne parkin)

Q05a During those three months did <>you<><>your <><> remain in bed or in a wheelchair for more than a week? **Q05a**

Response type: Single select from
Yes
No
Don't know

Response logic:
3 05b

Default next: 3 -06a
(Added 10/03/2003 02:09:02 PM by lparkin Modified 13/04/2003 03:17:40 PM by lparkin)

Q05b What was the reason for this? **Q05b**

Response type: Single line text
200
Default next: 3 -06a
(Added 10/03/2003 02:09:27 PM by lparkin Modified 20/03/2003 06:45:57 PM by lparkin)

Q06a During those three months, that is between the <> and the <>, <>were you<><>was your <><> taking any medication (excluding oral contraceptives and hormone replacement therapy)? **Q06a**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 06b

Default next: 3 -22a

(Added 10/03/2003 02:11:25 PM by lparkin Modified 22/05/2003 10:24:40 AM by lianne parkin)

Q06b IF MORE THAN ONE MEDICATION NAMED: I am going to ask you some questions about each medication. Lets take the first medication that <>you<><>your <><> took between the <> and the <>. **Q06b**

Response type: Statement

Default next: 3 -06c

(Added 16/04/2003 05:29:46 PM by lianne parkin Modified 13/05/2003 12:09:18 PM by lianne parkin)

Q06c What was the medication <>you were<><><>s<>he was<> taking? What was the name of the medicine? **Q06c**

Response type: Single line text

200

Default next: 3 -06d Start of Loop

(Added 13/03/2003 10:38:47 AM by lparkin Modified 11/05/2003 07:03:22 PM by lianne parkin)

Q06d Why <>were you<><>was <>s<>he<> taking this drug - what medical condition <>were you<><>was your <><> being treated for? **Q06d**

Response type: Multichoice from

Angina
Heart attack
Stroke
High blood pressure
Systemic lupus erythematosis
Crohn's disease or ulcerative colitis
Other heart problems
Diabetes
Kidney problems
Liver problems
Cancer
Superficial or deep vein thrombosis
Pulmonary embolism
Blood disorder which increased chances of clots
Other

Post-logic:

bittest(Qdata3.q06d,1) and Qdata1.q01=2 GOTO:3 07a
bittest(Qdata3.q06d,1) and Qdata1.q01=3 GOTO:3 07c
bittest(Qdata3.q06d,2) and Qdata1.q02=2 GOTO:3 08a
bittest(Qdata3.q06d,2) and Qdata1.q02=3 GOTO:3 08c
bittest(Qdata3.q06d,3) and Qdata1.q03=2 GOTO:3 09a
bittest(Qdata3.q06d,3) and Qdata1.q03=3 GOTO:3 09c
!Reference.ucontrol and Reference.umale and bittest(Qdata3.q06d,4) and Qdata1.q04=2 GOTO:3 10a
Reference.ucontrol and Reference.male and bittest(Qdata3.q06d,4) and Qdata1.q04=2 GOTO:3 10a
!Reference.ucontrol and Reference.ufemale and bittest(Qdata3.q06d,4) and Qdata1.q04=2 and Qdata2.q01c<>1 GOTO:3 10a
Reference.ucontrol and Reference.female and bittest(Qdata3.q06d,4) and Qdata1.q04=2 and Qdata2.q01c<>1 GOTO:3 10a
!Reference.ucontrol and Reference.umale and bittest(Qdata3.q06d,4) and Qdata1.q04=3 GOTO:3 10c
Reference.ucontrol and Reference.male and bittest(Qdata3.q06d,4) and Qdata1.q04=3 GOTO:3

10c
!Reference.ucontrol and Reference.ufemale and bittest(Qdata3.q06d,4) and Qdata1.q04=3 and Qdata2.q01c<>1 GOTO:3 10c
Reference.ucontrol and Reference.female and bittest(Qdata3.q06d,4) and Qdata1.q04=3 and Qdata2.q01c<>1 GOTO:3 10c
bittest(Qdata3.q06d,5) and Qdata1.q05=2 GOTO:3 11a
bittest(Qdata3.q06d,5) and Qdata1.q05=3 GOTO:3 11c
bittest(Qdata3.q06d,6) and Qdata1.q06=2 GOTO:3 12a
bittest(Qdata3.q06d,6) and Qdata1.q06=3 GOTO:3 12c
bittest(Qdata3.q06d,7) and Qdata1.q08a=2 GOTO:3 13a
bittest(Qdata3.q06d,7) and Qdata1.q08a=3 GOTO:3 13c
bittest(Qdata3.q06d,8) and Qdata1.q09a=2 GOTO:3 14a
bittest(Qdata3.q06d,8) and Qdata1.q09a=3 GOTO:3 14c
bittest(Qdata3.q06d,9)and Qdata1.q10a=2 GOTO:3 15a
bittest(Qdata3.q06d,9) and Qdata1.q10a=3 GOTO:3 15c
bittest(Qdata3.q06d,10) and Qdata1.q11a=2 GOTO:3 16a
bittest(Qdata3.q06d,10) and Qdata1.q11a=3 GOTO:3 16c
bittest(Qdata3.q06d,11) and Qdata1.q12a=2 GOTO:3 17a
bittest(Qdata3.q06d,11) and Qdata1.q12a=3 GOTO:3 17c
bittest(Qdata3.q06d,12) and Qdata1.q14a=2 GOTO:3 18a
bittest(Qdata3.q06d,12) and Qdata1.q14a=3 GOTO:3 18c
bittest(Qdata3.q06d,13) and Qdata1.q15a=2 GOTO:3 19a
bittest(Qdata3.q06d,13) and Qdata1.q15a=3 GOTO:3 19c
bittest(Qdata3.q06d,14) and Qdata1.q16a=2 GOTO:3 20a
bittest(Qdata3.q06d,14) and Qdata1.q16a=3 GOTO:3 20c
bittest(Qdata3.q06d,15) GOTO:3 06e

Default next: 3 -06f

(Added 10/03/2003 02:13:26 PM by lparkin Modified 14/05/2003 11:19:08 PM by lianne parkin)

Q06e (Record "other" indication for drug) **Q06e**

Response type: Single line text

200

Default next: 3 -06f

(Added 15/05/2003 09:37:24 AM by lianne parkin Modified / / : : AM by)

Q06f What is the drug code prefix? **Q06f**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:3 21

Response type: Numeric

99

Default next: 3 -06g

(Added 11/03/2003 06:43:04 PM by lparkin Modified 15/05/2003 09:38:47 AM by lianne parkin)

Q06g What is the drug code suffix? **Q06g**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:3 21

Response type: Numeric

999

Default next: 3 -21

(Added 11/03/2003 06:44:13 PM by lparkin Modified 15/05/2003 09:44:03 AM by lianne parkin)

Q07a Now I'd like to double check something. **Q07a**

You've just said that <>you were<><>your <> was<> given this medication to treat angina, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for angina before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated

for angina at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 07b

Default next: 3 -21

(Added 19/03/2003 04:09:00 PM by lparkin Modified 14/05/2003 09:32:54 PM by lianne parkin)

Q07b And <>were you<><>was <>s<>he<> given medication for angina during the three months between the <> and the <>? **Q07b**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 06f

Default next: 3 -21

(Added 08/04/2003 03:17:27 PM by lparkin Modified 14/05/2003 09:33:06 PM by lianne parkin)

Q07c Now I'd like to double check something. **Q07c**

You've just said that <>you were<><>your <> was<> given this medication to treat angina, BUT earlier you said that you didn't know whether <>you were<><><><>s<>he was<> treated for angina before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for angina at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 07d

Default next: 3 -21

(Added 01/04/2003 04:28:37 PM by lparkin Modified 14/05/2003 09:33:13 PM by lianne parkin)

Q07d And <>were you<><>was <>s<>he<> given medication for angina during the three months between the <> and the <>? **Q07d**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 06f

Default next: 3 -21

(Added 08/04/2003 03:30:08 PM by lparkin Modified 14/05/2003 09:33:21 PM by lianne parkin)

Q08a Now I'd like to double check something. **Q08a**

You've just said that <>you were<><>your <> was<> given this medication because <>you'd<><><>s<>he'd<> had a heart attack, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for a heart attack before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a heart attack at some time before the <>.

Response type: Single select from
True
False
Don't know

Response logic:
3 08b

Default next: 3 -21

(Added 24/03/2003 02:20:40 PM by lparkin Modified 14/05/2003 09:33:29 PM by lianne parkin)

Q08b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q08b**

Response type: Single select from
Yes
No
Don't know

Response logic:
3 06f

Default next: 3 -21

(Added 08/04/2003 03:46:35 PM by lparkin Modified 14/05/2003 09:33:47 PM by lianne parkin)

Q08c Now I'd like to double check something. **Q08c**

You've just said that <>you were<><>your <> was<> given this medication because <>you'd<><><>s<>he'd<> had a heart attack, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for a heart attack before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a heart attack at some time before the <>.

Response type: Single select from
True
False
Don't know

Response logic:
3 08d

Default next: 3 -21

(Added 01/04/2003 05:01:30 PM by lparkin Modified 14/05/2003 09:33:56 PM by lianne parkin)

Q08d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q08d**

Response type: Single select from
Yes
No
Don't know

Response logic:
3 06f

Default next: 3 -21

(Added 08/04/2003 03:49:44 PM by lparkin Modified 14/05/2003 09:34:04 PM by lianne parkin)

Q09a Now I'd like to double check something. **Q09a**

You've just said that <>you were<><>your <>

was<> given this medication because <>you'd<><><><>s<>he'd<> had a stroke BUT earlier you said that <>you WEREN'T<><><><>s<>he WASN'T<> treated for a stroke before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><><>Your <> WAS<> treated for a stroke at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 09b

Default next: 3 -21

(Added 24/03/2003 04:08:11 PM by lparkin Modified 14/05/2003 09:34:12 PM by lianne parkin)

Q09b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q09b**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 06f

Default next: 3 -21

(Added 08/04/2003 04:18:23 PM by lparkin Modified 14/05/2003 09:34:20 PM by lianne parkin)

Q09c Now I'd like to double check something. **Q09c**

You've just said that <>you were<><>your <> was<> given this medication because <>you'd<><><><>s<>he'd<> had a stroke, BUT earlier you said that you didn't know whether <>you were<><><><>s<>he was<> treated for a stroke before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><><>Your <> WAS<> treated for a stroke at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 09d

Default next: 3 -21

(Added 01/04/2003 05:09:10 PM by lparkin Modified 14/05/2003 09:34:28 PM by lianne parkin)

Q09d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q09d**

Response type: Single select from

Yes
No
Don't know

Response logic:
3 06f

Default next: 3 -21

(Added 08/04/2003 04:20:29 PM by lparkin Modified 14/05/2003 09:34:37 PM by lianne parkin)

Q10a Now I'd like to double check something. **Q10a**

You've just said that <>you were<><>your <> was<> given this medication to treat high blood pressure, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for high blood pressure before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for high blood pressure at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:
3 10b

Default next: 3 -21

(Added 24/03/2003 04:15:52 PM by lparkin Modified 14/05/2003 09:34:49 PM by lianne parkin)

Q10b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q10b**

Response type: Single select from

Yes
No
Don't know

Response logic:
3 06f

Default next: 3 -21

(Added 08/04/2003 04:22:43 PM by lparkin Modified 14/05/2003 09:34:57 PM by lianne parkin)

Q10c Now I'd like to double check something. **Q10c**

You've just said that <>you were<><>your <> was<> given this medication to treat high blood pressure, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for highblood pressure before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for high blood pressure at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:
3 10d

Default next: 3 -21

(Added 08/04/2003 04:24:30 PM by lparkin Modified 14/05/2003 09:35:07 PM by lianne parkin)

Q10d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q10d**

Response type: Single select from
Yes
No
Don't know

Response logic:
3 06f

Default next: 3 -21

(Added 08/04/2003 04:24:56 PM by lparkin Modified 14/05/2003 09:35:16 PM by lianne parkin)

Q11a Now I'd like to double check something. **Q11a**

You've just said that <>you were<><>your <> was<> given this medication to treat systemic lupus erythematosis, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for systemic lupus erythematosis before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for systemic lupus erythematosis at some time before the <>.

Response type: Single select from
True
False
Don't know

Response logic:
3 11b

Default next: 3 -21

(Added 24/03/2003 04:57:57 PM by lparkin Modified 14/05/2003 09:35:23 PM by lianne parkin)

Q11b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q11b**

Response type: Single select from
Yes
No
Don't know

Response logic:
3 06f

Default next: 3 -21

(Added 08/04/2003 04:28:33 PM by lparkin Modified 14/05/2003 09:35:31 PM by lianne parkin)

Q11c Now I'd like to double check something. **Q11c**

You've just said that <>you were<><>your <> was<> given this medication to treat systemic lupus erythematosis, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for systemic lupus erythematosis before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for systemic lupus erythematosis at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:
3 11d

Default next: 3 -21

(Added 02/04/2003 10:05:06 AM by lparkin Modified 14/05/2003 09:35:39 PM by lianne parkin)

Q11d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q11d**

Response type: Single select from

Yes
No
Don't know

Response logic:
3 06f

Default next: 3 -21

(Added 08/04/2003 04:30:20 PM by lparkin Modified 14/05/2003 09:35:46 PM by lianne parkin)

Q12a Now I'd like to double check something. **Q12a**

You've just said that <>you were<><>your <> was<> given this medication to treat Crohn's disease or ulcerative colitis , BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for either of these conditions before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for Crohn's disease or ulcerative colitis at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:
3 12b

Default next: 3 -21

(Added 24/03/2003 05:05:54 PM by lparkin Modified 14/05/2003 09:35:55 PM by lianne parkin)

Q12b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <>**Q12b** and the <>?

Response type: Single select from

Yes
No
Don't know

Response logic:
3 06f

Default next: 3 -21

(Added 08/04/2003 04:34:33 PM by lparkin Modified 14/05/2003 09:36:03 PM by lianne parkin)

Q12c Now I'd like to double check something. **Q12c**

You've just said that <>you were<><>your <>
was<> given this medication to treat Crohn's disease or ulcerative colitis, BUT earlier you said that you didn't know whether <>you
were<><><>s<>he was<> treated for either
of these conditions before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for Crohn's disease or ulcerative colitis at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 12d

Default next: 3 -21

(Added 02/04/2003 10:35:55 AM by lparkin Modified 14/05/2003 09:36:12 PM by lianne parkin)

Q12d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q12d**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 06f

Default next: 3 -21

(Added 08/04/2003 04:36:37 PM by lparkin Modified 14/05/2003 09:36:19 PM by lianne parkin)

Q13a Now I'd like to double check something. **Q13a**

You've just said that <>you were<><>your <> was<> given this medication to treat a heart problem, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated other heart problems before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a heart problem at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 13b

Default next: 3 -21

(Added 24/03/2003 05:09:31 PM by lparkin Modified 14/05/2003 10:19:20 PM by lianne parkin)

Q13b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q13b**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -13e

(Added 08/04/2003 04:47:02 PM by lparkin Modified 08/04/2003 05:53:36 PM by lparkin)

Q13c Now I'd like to double check something. **Q13c**

You've just said that <>you were<><>your <> was<> given this medication to treat a heart problem, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated other heart problems before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to

tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><><>Your <> WAS<> treated for a heart problem at some time before the <>.

Response type: Single select from

Yes
No
Don't know

Response logic:

3 13d

Default next: 3 -21

(Added 02/04/2003 10:50:57 AM by lparkin Modified 14/05/2003 10:19:34 PM by lianne parkin)

Q13d And <>were you<><><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q13d**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -13e

(Added 08/04/2003 04:47:43 PM by lparkin Modified 08/04/2003 05:53:55 PM by lparkin)

Q13e I'd like to ask you a question about the heart problem and then we'll return to the questions about medications. So: **Q13e**

What was the heart problem(s) <>you were<><><>your <> was<> treated for?

Response type: Single line text

200

Default next: 3 -13f

(Added 02/04/2003 11:18:26 AM by lparkin Modified 17/04/2003 12:09:44 PM by lianne parkin)

Q13f What is (are) the ICD code(s)? **Q13f**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:3 13g

Response type: Numeric

999.9

Default next: 3 -13g

(Added 02/04/2003 11:19:53 AM by lparkin Modified 14/05/2003 10:20:12 PM by lianne parkin)

Q13g (Continue) **Q13g**

Pre-logic: Qdata3.q13a=1 and Qdata3.q13b=1 GOTO:3 06f
Qdata3.q13c=1 and Qdata3.q13d=1 GOTO:3 06f
Qdata3.q13a=1 and Qdata3.q13b<>1 GOTO:3 21
Qdata3.q13c=1 and Qdata3.q13d<>1 GOTO:3 21

Response type: Statement

Default next: 3 -06f

(Added 17/04/2003 12:13:34 PM by lianne parkin Modified 14/05/2003 10:22:28 PM by lianne parkin)

Q14a Now I'd like to double check something. **Q14a**

You've just said that <>you were<><>your <> was<> given this medication to treat diabetes, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for diabetes before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for diabetes at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 14b

Default next: 3 -21

(Added 24/03/2003 05:14:22 PM by lparkin Modified 14/05/2003 09:37:03 PM by lianne parkin)

Q14b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q14b**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -14e

(Added 08/04/2003 04:50:54 PM by lparkin Modified 08/04/2003 05:54:20 PM by lparkin)

Q14c Now I'd like to double check something. **Q14c**

You've just said that <>you were<><>your <> was<> given this medication to treat diabetes, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for diabetes before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for diabetes at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 14d

Default next: 3 -21

(Added 02/04/2003 11:26:37 AM by lparkin Modified 14/05/2003 09:37:13 PM by lianne parkin)

Q14d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q14d**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -14e

(Added 08/04/2003 04:52:34 PM by lparkin Modified 08/04/2003 05:54:31 PM by lparkin)

Q14e I'd like to ask you a question about the diabetes and then we'll return to the questions about medications. So: **Q14e**

What type of diabetes did <>you<><>your <><> have?

PROMPT IF NECESSARY: <>Were you<><>Was <>s<>he<> treated with insulin injections, with tablets, or with a particular diet?

Response type: Single select from

Insulin dependent
Non-insulin dependent
Gestational diabetes only
Unknown

Post-logic: Qdata3.q14a=1 and Qdata3.q14b=1 GOTO:3 06f
Qdata3.q14c=1 and Qdata3.q14d=1 GOTO:3 06f
Qdata3.q14a=1 and Qdata3.q14b<>1 GOTO:3 21
Qdata3.q14c=1 and Qdata3.q14d<>1 GOTO:3 21

Default next: 3 -06f

(Added 02/04/2003 11:34:27 AM by lparkin Modified 14/05/2003 10:23:50 PM by lianne parkin)

Q15a Now I'd like to double check something. **Q15a**

You've just said that <>you were<><>your <> was<> given this medication to treat a kidney problem, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for kidney problems before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a kidney problem at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 15b

Default next: 3 -21

(Added 24/03/2003 05:18:06 PM by lparkin Modified 14/05/2003 09:37:23 PM by lianne parkin)

Q15b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q15b**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -15e

(Added 08/04/2003 04:54:52 PM by lparkin Modified 08/04/2003 05:54:45 PM by lparkin)

Q15c Now I'd like to double check something. **Q15c**

You've just said that <>you were<><>your <> was<> given this medication to treat a kidney problem, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for kidney problems before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a kidney problem at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 15d

Default next: 3 -21

(Added 02/04/2003 11:46:14 AM by lparkin Modified 14/05/2003 09:37:32 PM by lianne parkin)

Q15d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q15d**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -15e

(Added 08/04/2003 04:56:42 PM by lparkin Modified 08/04/2003 05:55:03 PM by lparkin)

Q15e I'd like to ask you a question about the kidney problem(s) and then we'll return to the questions about medications. So: **Q15e**

What was the kidney problem(s) <>you were<><><><>s<>he was<> treated for?

Response type: Single line text

200

Default next: 3 -15f

(Added 02/04/2003 01:47:09 PM by lparkin Modified 08/04/2003 05:33:56 PM by lparkin)

Q15f What is (are) the ICD code(s)? **Q15f**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:3 15g

Response type: Numeric

999.9

Default next: 3 -15g

(Added 02/04/2003 01:50:20 PM by lparkin Modified 11/05/2003 07:01:13 PM by lianne parkin)

Q15g (Continue) **Q15g**

Pre-logic: Qdata3.q15a=1 and Qdata3.q15b=1 GOTO:3 06f
Qdata3.q15c=1 and Qdata3.q15d=1 GOTO:3 06f
Qdata3.q15a=1 and Qdata3.q15b<>1 GOTO:3 21
Qdata3.q15c=1 and Qdata3.q15d<>1 GOTO:3 21

Response type: Statement

Default next: 3 -06f

(Added 11/05/2003 01:36:27 PM by lianne parkin Modified 14/05/2003 10:24:43 PM by lianne parkin)

Q16a Now I'd like to double check something. **Q16a**

You've just said that <>you were<><>your <> was<> given this medication to treat a liver problem, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for liver problems before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a liver problem at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 16b

Default next: 3 -21

(Added 24/03/2003 05:20:38 PM by lparkin Modified 14/05/2003 09:37:42 PM by lianne parkin)

Q16b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q16b**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -16e

(Added 08/04/2003 05:43:51 PM by lparkin Modified 08/04/2003 05:55:40 PM by lparkin)

Q16c Now I'd like to double check something. **Q16c**

You've just said that <>you were<><>your <> was<> given this medication to treat a liver problem, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for liver problems before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a liver problem at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 16d

Default next: 3 -21

(Added 02/04/2003 01:53:57 PM by lparkin Modified 14/05/2003 09:37:51 PM by lianne parkin)

Q16d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q16d**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -16e

(Added 08/04/2003 05:47:56 PM by lparkin Modified 11/05/2003 01:04:41 PM by lianne parkin)

Q16e I'd like to ask you a question about the liver problem(s) and then we'll return to the questions about medications. So: **Q16e**

What was the liver problem(s) <>you were<><><>s<>he was<> treated for?

Response type: Single line text

200

Default next: 3 -16f

(Added 02/04/2003 01:55:17 PM by lparkin Modified 08/04/2003 05:48:08 PM by lparkin)

Q16f What is (are) the ICD code(s)? **Q16f**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:3 16g

Response type: Numeric

999.9

Default next: 3 -16g

(Added 02/04/2003 01:56:23 PM by lparkin Modified 11/05/2003 01:40:06 PM by lianne parkin)

Q16g (Continue) **Q16g**

Pre-logic: Qdata3.q16a=1 and Qdata3.q16b=1 GOTO:3 06f
Qdata3.q16c=1 and Qdata3.q16d=1 GOTO:3 06f
Qdata3.q16a=1 and Qdata3.q16b<>1 GOTO:3 21
Qdata3.q16c=1 and Qdata3.q16d<>1 GOTO:3 21

Response type: Statement

Post-logic: Qdata3.q16a=1 and Qdata3.q16b=1 GOTO:3 06f
Qdata3.q16c=1 and Qdata3.q16d=1 GOTO:3 06f
Qdata3.q16a=1 and Qdata3.q16b<>1 GOTO:3 23
Qdata3.q16c=1 and Qdata3.q16d<>1 GOTO:3 23

Default next: 3 -06f

(Added 17/04/2003 12:23:07 PM by lianne parkin Modified 14/05/2003 10:25:24 PM by lianne parkin)

Q17a Now I'd like to double check something. **Q17a**

You've just said that <>you were<><>your <> was<> given this medication to treat cancer, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for cancer before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for cancer at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 17b

Default next: 3 -21

(Added 24/03/2003 05:23:02 PM by lparkin Modified 14/05/2003 09:38:01 PM by lianne parkin)

Q17b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q17b**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -17e

(Added 08/04/2003 05:52:02 PM by lparkin Modified / / : : AM by)

Response type: Single select from

Yes
No
Don't know

Default next: 3 -17e

(Added 08/04/2003 05:57:20 PM by lparkin Modified / / : : AM by)

Q17c Now I'd like to double check something. **Q17c**

You've just said that <>you were<><>your <> was<> given this medication to treat cancer, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for cancer before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for cancer at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 17d

Default next: 3 -21

(Added 02/04/2003 02:01:44 PM by lparkin Modified 14/05/2003 09:38:14 PM by lianne parkin)

Q17d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q17d**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -17e

(Added 08/04/2003 05:59:10 PM by lparkin Modified / / : : AM by)

Q17e I'd like to ask you a few short questions about the cancer and then we'll return to the questions about medications. So: **Q17e**

What type(s) of cancer did <>you <><><>s<>he<> have?

NB. IF BONE, BRAIN, OR LIVER CANCER STATED, ASK: Where did the cancer start?

IF SKIN CANCER STATED, ASK: Was it a melanoma skin cancer?

Response type: Single line text

200

Default next: 3 -17f

(Added 02/04/2003 02:04:26 PM by lparkin Modified 11/05/2003 01:48:06 PM by lianne parkin)

Q17f When was the cancer first diagnosed? **Q17f**

Response type: Single line text

200

Default next: 3 -17g

(Added 02/04/2003 02:05:10 PM by lparkin Modified 10/05/2003 03:57:53 PM by lianne parkin)

Q17g What is (are) the ICD code(s)? **Q17g**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:3 17h

Response type: Numeric

999.9

Default next: 3 -17h

(Added 02/04/2003 02:05:26 PM by lparkin Modified 11/05/2003 01:44:24 PM by lianne parkin)

Q17h Now I'm going to continue with the questions about medications. **Q17h**

Response type: Statement

Post-logic: Qdata3.q17a=1 and Qdata3.q17b=1 GOTO:3 06f
Qdata3.q17c=1 and Qdata3.q17d=1 GOTO:3 06f
Qdata3.q17a=1 and Qdata3.q17b<>1 GOTO:3 21
Qdata3.q17c=1 and Qdata3.q17d<>1 GOTO:3 21

Default next: 3 -06f

(Added 02/04/2003 02:06:51 PM by lparkin Modified 14/05/2003 10:26:26 PM by lianne parkin)

Q18a Now I'd like to double check something. **Q18a**

You've just said that <>you were<><>your <> was<> given this medication to treat a blood clot in the veins of the leg, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for blood clots before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a blood clot in the veins of the leg at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 18b

Default next: 3 -21

(Added 24/03/2003 05:27:01 PM by lparkin Modified 14/05/2003 09:38:25 PM by lianne parkin)

Response type: Single select from

True
False
Don't know

Response logic:

3 18b

Default next: 3 -21

(Added 09/04/2003 01:39:38 PM by lparkin Modified 14/05/2003 09:38:33 PM by lianne parkin)

Q18b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q18b**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -18e

(Added 08/04/2003 06:03:54 PM by lparkin Modified / / : : AM by)

Q18c Now I'd like to double check something. **Q18c**

You've just said that <>you were<><>your <> was<> given this medication to treat a blood clot in the legs, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for blood clots before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a blood clot in the legs at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 18d

Default next: 3 -21

(Added 02/04/2003 02:11:05 PM by lparkin Modified 14/05/2003 09:38:48 PM by lianne parkin)

Q18d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q18d**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -18e

(Added 08/04/2003 06:24:10 PM by lparkin Modified / / : : AM by)

Q18e I'd like to ask you a few short questions about the blood clot and then we'll return to the questions about medications. So: **Q18e**

Was the blood clot in the veins on the SURFACE of your <><>'s<> leg, OR in the DEEP VEINS of <>your<><><>her<><>his<</Umale>><> leg?

PROMPT IF NECESSARY: The medical names for blood clots in the veins on the surface of the legs are superficial venous thrombosis or thrombophlebitis; and the medical name for blood clots in the deep veins of the legs or pelvis is deep vein thrombosis, or DVT or short.

Response type: Single select from

Superficial only
Deep only
Both, concurrently
Both, at different times
Don't know

Post-logic: Qdata3.q18e=1 or Qdata3.q18e=3 or Qdata3.q18e=4 GOTO:3 18f
Qdata3.q18e=2 GOTO:3 18k
Qdata3.q18e=5 GOTO:3 18q

Default next: 3 -21

(Added 02/04/2003 02:13:48 PM by lparkin Modified 14/05/2003 09:39:03 PM by lianne parkin)

Q18f I'd like to ask you some more questions about the clot in the veins on the SURFACE of your <><>'s<> leg. **Q18f**

When was the (first episode if > 1) clot diagnosed?

Response type: Single line text

200

Default next: 3 -18g

(Added 02/04/2003 02:19:09 PM by lparkin Modified 11/05/2003 02:12:21 PM by lianne parkin)

Q18g <>Were you<><>Was your <><> treated for the (first episode if > 1) clot? **Q18g**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 18h

Default next: 3 -18i

(Added 02/04/2003 02:20:38 PM by lparkin Modified 08/04/2003 06:05:54 PM by lparkin)

Q18h What treatment <>were you<><> was <>s<>he<> given? **Q18h**

READ OUT IF NECESSARY AND SELECT AS MANY AS APPLY (scroll down):
1. A drug to thin the blood that was given through an intravenous drip or injected under the skin (heparin or low molecular weight heparin)
2. Pills to thin the blood such as warfarin or coumarin (usually given for at least 3 months)
3. Aspirin or other pills (other than warfarin / coumarin) that help to thin the blood
4. Anti-inflammatory pills
5. Antibiotic pills
6. Ointments
7. Bed rest
8. Other

Response type: Multichoice from

Heparin / LMWH
Warfarin / coumarin
Aspirin or other pills
Anti-inflammatories
Antibiotics
Ointments
Bed rest
Other

Default next: 3 -18i

(Added 02/04/2003 02:53:26 PM by lparkin Modified 11/05/2003 02:14:47 PM by lianne parkin)

Q18i Did the (first episode if > 1) clot occur at any particular time, for example: **Q18i**
<><>During pregnancy?
After giving birth?<><>
<><>During pregnancy?
After giving birth?<><>
After an operation?
After an injury?
During an illness?

Response type: Single select from

Yes
No
Don't know

Response logic:

3 18j

Default next: 3 -18k

(Added 02/04/2003 02:55:08 PM by lparkin Modified 13/05/2003 09:59:51 PM by lianne parkin)

Q18j What were the circumstances? **Q18j**

Response type: Multichoice from

Pregnancy / puerperium
Postoperative
Injury
Illness
Other

Default next: 3 -18k

(Added 02/04/2003 02:57:00 PM by lparkin Modified 08/04/2003 06:08:37 PM by lparkin)

Q18k I'd like to ask you some more questions about the clot in the DEEP veins of your <><>'s<> leg. **Q18k**

Pre-logic: Qdata3.q18e=1 GOTO:3 18v
Response type: Statement
Default next: 3 -18l

(Added 02/04/2003 04:44:53 PM by lparkin Modified 13/05/2003 10:34:00 PM by lianne parkin)

Q18l When was the (first episode if > 1) clot in the DEEP veins of your legs diagnosed? The medical name for this condition is deep vein thrombosis. **Q18l**

Pre-logic: Qdata3.q18c=1 GOTO:3 18t
Response type: Single line text
Default next: 3 -18m

(Added 02/04/2003 02:59:17 PM by lparkin Modified 08/04/2003 06:09:49 PM by lparkin)

Q18m <>Were you<><>Was your <> <> given treatment for the deep vein thrombosis? **Q18m**

Response type: Single select from

Yes
No
Don't know

Response logic:
3 18n

Default next: 3 -18o

(Added 02/04/2003 03:03:00 PM by lparkin Modified 08/04/2003 06:10:27 PM by lparkin)

Q18n What treatment <>were you<><>was <>s<>he <> given? **Q18n**

READ OUT IF NECESSARY AND SELECT AS MANY AS APPLY (scroll down):
1. A drug to thin the blood that was given through an intravenous drip or injected under the skin (heparin or low molecular weight heparin)
2. Pills to thin the blood such as warfarin or coumarin (usually given for at least 3 months)
3. Aspirin or other pills (other than warfarin / coumarin) that help to thin the blood
4. Anti-inflammatory pills
5. Antibiotic pills
6. Ointments
7. Bed rest
8. Other

Response type: Multichoice from

Heparin / LMWH
Warfarin / coumarin
Aspirin or other pills
Anti-inflammatories
Antibiotics
Ointments
Bed rest
Other

Default next: 3 -18o

(Added 02/04/2003 03:04:17 PM by lparkin Modified 11/05/2003 02:15:02 PM by lianne parkin)

Q18o Did the (first episode if > 1) deep vein thrombosis occur at any particular time, for example: **Q18o**

<><>During pregnancy?
After giving birth?<><>
<><>During pregnancy?
After giving birth?<><>
After an operation?
After an injury?
During an illness?

Response type: Single select from

Yes
No
Don't know

Response logic:

3 18p

Default next: 3 -18v

(Added 02/04/2003 03:06:24 PM by lparkin Modified 11/05/2003 02:19:45 PM by lianne parkin)

Q18p What were the circumstances? **Q18p**

Response type: Multichoice from

Pregnancy / puerperium
Postoperative
Injury
Illness
Other

Default next: 3 -18v

(Added 02/04/2003 03:06:31 PM by lparkin Modified 08/04/2003 06:21:07 PM by lparkin)

Q18q When was the clot (first episode if > 1) diagnosed? **Q18q**

Response type: Single line text

200

Default next: 3 -18r

(Added 02/04/2003 03:07:22 PM by lparkin Modified 13/05/2003 09:58:52 PM by lianne parkin)

Q18r <>Were you<><>Was your <><> given treatment for the (first episode if > 1) clot? **Q18r**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 18s

Default next: 3 -18t

(Added 02/04/2003 03:14:35 PM by lparkin Modified 08/04/2003 06:13:22 PM by lparkin)

Q18s What treatment <>were you<><>was <>s<>he<> given? **Q18s**

READ OUT IF NECESSARY AND SELECT AS MANY AS APPLY (scroll down):
1. A drug to thin the blood that was given through an intravenous drip or injected under the skin (heparin or low molecular weight heparin)
2. Pills to thin the blood such as warfarin or coumarin (usually given for at least 3 months)
3. Aspirin or other pills (other than warfarin / coumarin) that help to thin the blood
4. Anti-inflammatory pills
5. Antibiotic pills
6. Ointments
7. Bed rest
8. Other

Response type: Single select from

Heparin / LMWH
Warfarin / coumarin
Aspirin or other pills
Anti-inflammatories
Antibiotics
Ointments
Bed rest

Other

Default next: 3 -18t

(Added 02/04/2003 03:16:01 PM by lparkin Modified 11/05/2003 02:15:14 PM by lianne parkin)

Q18t Did the (first episode if > 1)) clot occur at any particular time, for example: **Q18t**
<><>During pregnancy?
After giving birth?<><>
<><>During pregnancy?
After giving birth?<><>
After an operation?
After an injury?
During an illness?

Response type: Single select from
Yes
No
Don't know

Response logic:
3 18u

Default next: 3 -18v

(Added 02/04/2003 03:17:14 PM by lparkin Modified 11/05/2003 02:19:59 PM by lianne parkin)

Q18u What were the circumstances? **Q18u**

Response type: Single select from
Pregnancy / puerperium
Postoperative
Injury
Illness
Other

Default next: 3 -18v

(Added 02/04/2003 03:18:16 PM by lparkin Modified 08/04/2003 06:20:41 PM by lparkin)

Q18v Now I'm going to continue with the questions about medications. **Q18v**

Response type: Statement

Post-logic: Qdata3.q18a=1 and Qdata3.q18b=1 GOTO:3 06f
Qdata3.q18c=1 and Qdata3.q18d=1 GOTO:3 06f
Qdata3.q18a=1 and Qdata3.q18b<>1 GOTO:3 21
Qdata3.q18c=1 and Qdata3.q18d<>1 GOTO:3 21

Default next: 3 -06f

(Added 02/04/2003 03:19:12 PM by lparkin Modified 14/05/2003 10:27:19 PM by lianne parkin)

Q19a Now I'd like to double check something. **Q19a**

You've just said that <>you were<><>your <> was<> given this medication to treat pulmonary embolism, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated for pulmonary embolism before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for pulmonary embolism at some time before the <>.

Response type: Single select from
True
False
Don't know

Response logic:
3 19b

Default next: 3 -21

(Added 24/03/2003 05:30:46 PM by lparkin Modified 14/05/2003 09:39:24 PM by lianne parkin)

Q19b And <>were you<><>was **Q19b**

<>s<>he<> given medication for this during the three months between the <> and the <>?

Response type: Single select from

Yes
No
Don't know

Default next: 3 -19e

(Added 09/04/2003 01:43:41 PM by lparkin Modified / / : : AM by)

Q19c Now I'd like to double check something. **Q19c**

You've just said that <>you were<><>your <> was<> given this medication to treat pulmonary embolism, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for pulmonary embolism before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for pulmonary embolism at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 19d

Default next: 3 -21

(Added 02/04/2003 03:34:06 PM by lparkin Modified 14/05/2003 09:39:35 PM by lianne parkin)

Q19d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q19d**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -19e

(Added 09/04/2003 01:45:42 PM by lparkin Modified / / : : AM by)

Q19e I'd like to ask you a few short questions about the pulmonary embolism and then we'll return to the questions about medications. So: **Q19e**

When was the (first episode if > 1) pulmonary embolism diagnosed?

Response type: Single line text

200

Default next: 3 -19f

(Added 02/04/2003 03:34:18 PM by lparkin Modified 09/04/2003 01:46:12 PM by lparkin)

Q19f <>Were you<><>Was your <><> treated with medication to thin the blood (heparin, warfarin, coumarin)? **Q19f**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -19g

(Added 02/04/2003 04:08:05 PM by lparkin Modified 09/04/2003 01:48:11 PM by lparkin)

Q19g Did the (first episode if > 1) pulmonary embolism occur at any particular time, for example: **Q19g**
<><>During pregnancy?
After giving birth?<><>
<><>During pregnancy?
After giving birth?<><>
After an operation?
After an injury?
During an illness?

Response type: Single select from
Yes
No
Don't know

Response logic:
3 19h

Default next: 3 -19i

(Added 02/04/2003 04:09:12 PM by lparkin Modified 11/05/2003 02:21:45 PM by lianne parkin)

Q19h What were the circumstances? **Q19h**

Response type: Single select from
Pregnancy / puerperium
Postoperative
Injury
Illness
Other

Default next: 3 -19i

(Added 02/04/2003 04:38:57 PM by lparkin Modified 09/04/2003 01:48:25 PM by lparkin)

Q19i Now I'm going to continue with the questions about medications. **Q19i**

Response type: Statement

Post-logic: Qdata3.q19a=1 and Qdata3.q19b=1 GOTO:3 06f
Qdata3.q19c=1 and Qdata3.q19d=1 GOTO:3 06f
Qdata3.q19a=1 and Qdata3.q19b<>1 GOTO:3 21
Qdata3.q19c=1 and Qdata3.q19d<>1 GOTO:3 21

Default next: 3 -06f

(Added 03/04/2003 10:00:25 AM by lparkin Modified 14/05/2003 10:27:50 PM by lianne parkin)

Q20a Now I'd like to double check something. **Q20a**

You've just said that <>you were<><>your <> was<> given this medication to treat a blood disorder which increased the chances of developing a deep vein thrombosis or pulmonary embolism, BUT earlier you said that <>you WEREN'T<><><>s<>he WASN'T<> treated such a condition before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a blood disorder which increased the chances of developing a deep vein thrombosis or pulmonary embolism at some time before the <>.

Response type: Single select from
True
False
Don't know

Response logic:
3 20b

Default next: 3 -21

(Added 24/03/2003 05:34:12 PM by lparkin Modified 14/05/2003 09:39:46 PM by lianne parkin)

Q20b And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q20b**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -20e

(Added 09/04/2003 03:30:24 PM by lparkin Modified 09/04/2003 03:32:16 PM by lparkin)

Q20c Now I'd like to double check something. **Q20c**

You've just said that <>you were<><>your <> was<> given this medication to treat a blood disorder which increased the chances of developing a deep vein thrombosis or pulmonary embolism, BUT earlier you said that you didn't know whether <>you were<><><>s<>he was<> treated for such a condition before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false.

This is the sentence:

<>You WERE<><>Your <> WAS<> treated for a blood disorder which increased the chances of developing a deep vein thrombosis or pulmonary embolism at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 20d

Default next: 3 -21

(Added 03/04/2003 10:02:21 AM by lparkin Modified 14/05/2003 09:39:55 PM by lianne parkin)

Q20d And <>were you<><>was <>s<>he<> given medication for this during the three months between the <> and the <>? **Q20d**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -20e

(Added 09/04/2003 03:32:45 PM by lparkin Modified / / : : AM by)

Q20e I'd like to ask you a question about the blood disorder and then we'll return to the questions about medications. So: **Q20e**

I am going to read out the names of some disorders. I would like you to tell me if <>you were<><>your <> was <>diagnosed with any of these disorders: .
Record name(s) of disorder(s) if known, otherwise record unknown

Response type: Multichoice from

Factor V Leiden
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Dysfibrinogenaemia
Plasminogen deficiency
Prothrombin 20210A
High factor VIII
Increased platelets
Homocystinuria
Antiphospholipid syndrome
Anticardiolipin antibodies/ lupus anticoagulant
Unknown

VTE risk factors in the three months before the index date

Post-logic: Qdata3.q20a=1 and Qdata3.q20b=1 GOTO:3 06f
Qdata3.q20c=1 and Qdata3.q20d=1 GOTO:3 06f
Qdata3.q20a=1 and Qdata3.q20b<>1 GOTO:3 21
Qdata3.q20c=1 and Qdata3.q20d<>1 GOTO:3 21

Default next: 3 -06f

(Added 03/04/2003 10:05:32 AM by lparkin Modified 14/05/2003 10:28:26 PM by lianne parkin)

Q21 <>Were you<><>Was your <><> taking any other medications during the three months between the <> and the <>? **Q21**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 06c

Default next: 3 -22a End of Loop

(Added 11/03/2003 06:47:35 PM by lparkin Modified 15/05/2003 09:44:54 AM by lianne parkin)

Q22a During those three months, that is between the <> and the <>, <>did you<><>did your <><> smoke at least one cigarette a day? **Q22a**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 23

Default next: 3 -22b

(Added 10/03/2003 02:18:34 PM by lparkin Modified 14/05/2003 09:17:03 PM by lianne parkin)

Q22b Before the <>, <>did you<><>did <>s<>he<> EVER smoke at least one cigarette a day? **Q22b**

Response type: Single select from

Yes
No
Don't know

Default next: 3 -23

(Added 20/03/2003 11:52:29 AM by lparkin Modified 14/05/2003 09:17:17 PM by lianne parkin)

Q23 Now I would like to ask you a few questions about pregnancy and female hormones that <>you<><>you<><> might have taken in the three months between the <> and the <>. We are interviewing people of different ages, so some of these questions may appear strange for someone of your <><>'s <> age. **Q23**

Pre-logic: (Reference.ucontrol and Reference.male) or (!Reference.ucontrol and Reference.umale) GOTO:4a00

Response type: Statement

Default next: 3 -24a

(Added 10/03/2003 02:26:21 PM by lparkin Modified 14/05/2003 09:17:31 PM by lianne parkin)

Q24a <>Were you<><>Was your <><> pregnant at any time between the <> and the <>? **Q24a**

Pre-logic: (Reference.ucontrol and Reference.male) or (! Reference.ucontrol and Reference.umale) GOTO:400

Response type: Single select from

Yes
No
Don't know

Response logic:

3 24b

Default next: 3 -25a

(Added 10/03/2003 02:29:14 PM by lparkin Modified 14/05/2003 09:17:48 PM by lianne parkin)

<>Were you<><>Was she<> still pregnant on the

Q24b Q24b

<>?

Response type: Single select from

Yes
No
Don't know

Response logic:

3 25a

Default next: 3 -24c

(Added 28/03/2003 09:46:38 AM by lparkin Modified 14/05/2003 09:18:17 PM by lianne parkin)

Q24c On what date did <>your<><>her<> pregnancy end? (record date / don't know) Q24c

Response type: Single line text

200

Default next: 3 -24d

(Added 10/03/2003 02:31:37 PM by lparkin Modified 14/05/2003 09:18:59 PM by lianne parkin)

Q24d How many weeks pregnant <>were you<><>was she<> when the pregancy ended? (record number of weeks, or -2 if don't know) Q24d

PROMPT IF NECESSARY: A normal full term pregnancy is about 40 weeks

Response type: Numeric

99.9

Default next: 3 -24e

(Added 10/03/2003 02:33:19 PM by lparkin Modified 14/05/2003 09:19:13 PM by lianne parkin)

Q24e <>Were you<><>Was your <><> admitted to hospital at that time? Q24e

Response type: Single select from

Yes
No
Don't know

Response logic:

3 24f

Default next: 3 -25a

(Added 10/03/2003 02:36:51 PM by lparkin Modified 14/05/2003 09:19:29 PM by lianne parkin)

Q24f What hospital <>were you<><>was she<> admitted to? (record name of hospital / don't know) Q24f

Response type: Single line text

200

Default next: 3 -25a

(Added 03/04/2003 04:44:23 PM by lparkin Modified 14/05/2003 09:19:42 PM by lianne parkin)

Q25a Did <>you<><>your <><> take the oral contraceptive pill (the pill) at any time between the <> and the <>? Q25a

Response type: Single select from

Yes
No
Don't know

Response logic:

Post-logic: Qdata2.q02=1 and Qdata3.q25a=1 GOTO:3 25f
Qdata2.q02=2 and Qdata3.q25a=1 GOTO:3 25b
Qdata2.q02=2 and Qdata3.q25a=3 GOTO:3 25c
Qdata2.q02=3 and Qdata3.q25a=1 GOTO:3 25d

Default next: 3 -26a

(Added 10/03/2003 02:38:26 PM by lparkin Modified 15/05/2003 05:00:28 PM by lianne parkin)

Q25b Now I'd like to double check something. Q25b

You've just said that <>you<><>your <><>

DID take the oral contraceptive pill in the three months between the <> and the <>, BUT earlier you said that <>you<><>your <> <> HAD NEVER taken the pill before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false. This is the sentence:

<>You<><>Your <><> DID take the oral contraceptive pill at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 25e

Default next: 3 -26a

(Added 25/03/2003 04:40:38 PM by lparkin Modified 14/05/2003 09:23:55 PM by lianne parkin)

Q25c Now I'd like to double check something. **Q25c**

You've just said that you DON'T KNOW whether <>you <><>your <><> took the oral contraceptive pill in the three months between the <> and the <>, BUT earlier you said that <>you<><>she<> HAD NEVER taken the pill before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false. This is the sentence:

<>You<><>Your <><> DID take the oral contraceptive pill at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 25e

Default next: 3 -26a

(Added 28/03/2003 02:14:08 PM by lparkin Modified 15/05/2003 05:01:28 PM by lianne parkin)

Q25d Now I'd like to double check something. **Q25d**

You've just said that <>you <><>your <><> DID take the oral contraceptive pill in the three months between the <> and the <>, BUT earlier you said that you DIDN'T KNOW whether <>you<><>your <> <> had ever taken the pill before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false. This is the sentence:

<>You<><>Your <><> DID take the oral contraceptive pill at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 25e

Default next: 3 -26a

(Added 25/03/2003 04:19:14 PM by lparkin Modified 15/05/2003 05:01:50 PM by lianne parkin)

Q25e And did <>you<><>she<> take the pill in the three months between the <> and the <>? **Q25e**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 25f

Default next: 3 -26a

(Added 16/04/2003 12:01:25 PM by lianne parkin Modified 14/05/2003 09:25:01 PM by lianne parkin)

Q25f Do you remember the name of <>your<><>her<> pill? (record name of pill / don't know) **Q25f**

Response type: Single line text

200

Default next: 3 -25g

(Added 10/03/2003 02:39:59 PM by lparkin Modified 14/05/2003 09:25:25 PM by lianne parkin)

Q25g What is the drug code prefix? **Q25g**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:3 26a

Response type: Numeric

99

Default next: 3 -25h

(Added 14/05/2003 09:14:41 PM by lianne parkin Modified 15/05/2003 04:45:34 PM by lianne parkin)

Q25h What is the drug code suffix? **Q25h**

Response type: Numeric

999

Default next: 3 -26a

(Added 14/05/2003 09:15:08 PM by lianne parkin Modified 14/05/2003 09:26:13 PM by lianne parkin)

Q26a Did <>you<><>your <><> take hormone replacement therapy at any time between the <> and the <>? **Q26a**

PROMPT IF NECESSARY: By hormone replacement therapy I mean the female hormone pills, skin patches, or implants that some women use around the time of the menopause or the change of life.

Response type: Single select from

Yes
No
Don't know

Response logic:

Post-logic: Qdata2.q03=1 and Qdata3.q26a=1 GOTO:3 26f
Qdata2.q03=2 and Qdata3.q26a=1 GOTO:3 26b
Qdata2.q03=2 and Qdata3.q26a=3 GOTO:3 26c
Qdata2.q03=3 and Qdata3.q26a=1 GOTO:3 26d

Default next: 4a-00

(Added 10/03/2003 02:38:26 PM by lparkin Modified 15/05/2003 05:03:32 PM by lianne parkin)

Q26b Now I'd like to double check something. **Q26b**

You've just said that <>you<><>your <><> DID take hormone replacement therapy in the three months between the <> and the <>, BUT earlier you said that <>you<><>your <> <> HAD NEVER taken hormone replacement therapy before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false. This is the sentence:

<>You<><>Your <><> DID take hormone replacement therapy at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 26e

Default next: 4a-00

(Added 31/03/2003 11:39:00 AM by lparkin Modified 14/05/2003 09:30:02 PM by lianne parkin)

Q26c Now I'd like to double check something. **Q26c**

You've just said that you DON'T KNOW whether <>you <><>your <><> took hormone replacement therapy in the three months between the <> and the <>, BUT earlier you said that <>you<><>she<> HAD NEVER taken hormone replacement therapy before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false. This is the sentence:

<>You<><>Your <><> DID take hormone replacement therapy at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 26e

Default next: 4a-00

(Added 31/03/2003 11:41:14 AM by lparkin Modified 14/05/2003 09:30:25 PM by lianne parkin)

Q26d Now I'd like to double check something. **Q26d**

You've just said that <>you <><>your <><> DID take hormone replacement therapy in the three months between the <> and the <>, BUT earlier you said that you DIDN'T KNOW whether <>you<><>your <> <> had ever taken hormone replacement therapy before the <>.

I know that it's difficult to remember so far back, but I'm going to read out a sentence and I'd like you to tell me whether you think it is true or false. This is the sentence:

<>You<><>Your <><> DID take hormone replacement therapy at some time before the <>.

Response type: Single select from

True
False
Don't know

Response logic:

3 26e

Default next: 4a-00

(Added 06/04/2003 03:58:30 PM by lparkin Modified 14/05/2003 09:30:51 PM by lianne parkin)

Q26e And did <>you<><>she<> take hormone replacement therapy in the three months between the <> and the <>? **Q26e**

Response type: Single select from

Yes
No
Don't know

Response logic:

3 26f

Default next: 4a-00

(Added 16/04/2003 04:54:47 PM by lianne parkin Modified 15/05/2003 04:48:55 PM by lianne parkin)

Q26f What is the drug code prefix? **Q26f**

Pre-logic: lower(gcusername)<>'lianne parkin' GOTO:4a00

Response type: Numeric

99

Default next: 3 -26g

(Added 15/05/2003 04:47:45 PM by lianne parkin Modified 15/05/2003 05:02:46 PM by lianne parkin)

Q26g What is the drug code suffix? **Q26g**

Response type: Numeric

999

Default next: 4a-00

(Added 15/05/2003 04:48:20 PM by lianne parkin Modified 15/05/2003 05:02:56 PM by lianne parkin)

First international flight during the four weeks before the index date

Q00 Now I am going to ask you some questions about your <><>'s<> activities in the four weeks before the <>. **Q00**

If you look at your calendar you'll see that I'm referring to the weeks between the <> and the <>.

So:

Response type: Statement

Default next: 4a-01

(Added 14/03/2003 09:37:35 AM by lparkin Modified 17/04/2003 11:46:50 AM by lianne parkin)

Q01 Did <>you<><>your <><> go on any international flights during those four weeks? **Q01**

You may need to look at passports and other records before you can answer this question. Or you may need to talk to relatives or friends. I am happy to wait while you do this, or we can arrange a time for me to phone you back.

PROMPT IF NECESSARY: By international flights I mean flights out of New Zealand, flights into New Zealand from another country, and flights between countries other than New Zealand.

Response type: Single select from

Yes
No
Don't know

Response logic:

4a02

Default next: 9a-00a

(Added 13/03/2003 05:02:02 PM by lparkin Modified 16/04/2003 10:45:08 AM by lianne parkin)

Q02 IF MORE THAN ONE INTERNATIONAL FLIGHT DURING FOUR WEEK PERIOD: I am going to ask you some questions about each flight. Lets take the first INTERNATIONAL flight that <>you<><>your <><> had between the <> and the <>. **Q02**

From which INTERNATIONAL airport did your<> <>'s<> flight depart?
(record name / don't know)

Response type: Single line text

200

Default next: 4a-03

(Added 13/03/2003 05:08:15 PM by lparkin Modified 11/05/2003 07:09:07 PM by lianne parkin)

Q03 On what date did <>you<><>your <><> depart from this international airport? **Q03**
(record dd/mm/yy [local time] / don't know)

Response type: Single line text

200

Default next: 4a-04

(Added 11/03/2003 09:43:02 AM by lparkin Modified 11/05/2003 03:25:39 PM by lianne parkin)

Q04 At which airport did your<> <>'s<> international flight arrive? **Q04**
(record name of final destination / don't know)

PROMPT IF NECESSARY: Where did your <><>'s<> journey end?

Response type: Single line text

200

Default next: 4a-05

(Added 24/03/2003 10:32:21 AM by lparkin Modified 11/05/2003 07:06:37 PM by lianne parkin)

Q05 On what date did <>you<><>your <><> arrive at this airport? **Q05**
(record dd/mm/yy [local time] / don't know)

Response type: Single line text

200

Default next: 4a-06

(Added 11/03/2003 09:45:51 AM by lparkin Modified 11/04/2003 05:15:17 PM by lparkin)

Q06 Did the aeroplane land anywhere between _____ (international airport where began journey) and _____ (final destination)? **Q06**

Response type: Single select from

Yes
No
Don't know

Response logic:

4a12

Default next: 4a-07

(Added 11/03/2003 10:13:55 AM by lparkin Modified 13/04/2003 05:10:50 PM by lparkin)

Q07 How long was the flight between _____ (international airport from which departed) and _____ (final destination)? **Q07**
(record hours, or minutes, or "-2" if don't know)

Response type: Text entry with input mask

xx.xhrs(xxm)

Post-logic: alltrim(QData4a.q07)="-2" GOTO:4a08

Default next: 4a-09

(Added 13/04/2003 05:09:11 PM by lparkin Modified 20/05/2003 11:19:34 AM by lianne parkin)

Q08 Do you think it would have been less than 4 hours, between 4 to 8 hours, between 9 to 12 hours, or more than 12 hours? **Q08**

Response type: Single select from

Less than 4 hours
4 - 8 hours
9 -12 hours
More than 12 hours
Don't know

Default next: 4a-09

(Added 11/03/2003 10:41:36 AM by lparkin Modified 13/04/2003 05:13:26 PM by lparkin)

Q09 Which class <>were you<><>was your <><> travelling in? **Q09**

PROMPT IF NECESSARY: Was it first class, business class, economy class, or some other class?

Response type: Single select from

First
Business
Economy
Other
Don't know

Default next: 4a-10

(Added 11/03/2003 10:06:47 AM by lparkin Modified 13/04/2003 05:13:39 PM by lparkin)

Q10 Did <>you<><>your <><> have a seat on the aisle? **Q10**

Response type: Single select from

Yes
No
Don't know

Default next: 4a-11

(Added 11/03/2003 10:09:54 AM by lparkin Modified 15/04/2003 10:30:04 AM by lparkin)

Q11 Did <>you<><>your <><> take any sleeping pills immediately before, or during, the flight? **Q11**

Response type: Single select from

Yes
No
Don't know

Default next: 4a-26

(Added 11/03/2003 09:48:41 AM by lparkin Modified 15/04/2003 10:37:04 AM by lparkin)

Q12 Where did the aeroplane land? **Q12**
(record name of airport / don't know)

Response type: Single line text

200

Default next: 4a-13 Start of Loop

(Added 11/03/2003 10:21:31 AM by lparkin Modified 13/04/2003 06:16:10 PM by lparkin)

Q13 How long was the flight between _____ (airport from which departed on this leg of journey) and _____ (airport at which arrived on this leg of journey)? **Q13**
(record hours, or minutes, or "-2" if don't know)

Response type: Text entry with input mask

xx.xhrs(xxm)

Post-logic: alltrim(QData4a.q13) ="-2" GOTO:4a14

Default next: 4a-15

(Added 13/03/2003 05:53:12 PM by lparkin Modified 20/05/2003 11:20:10 AM by lianne parkin)

Q14 Do you think it would have been less than 4 hours, between 4 to 8 hours, between 9 to 12 hours, or more than 12 hours? **Q14**

Response type: Single select from

Less than 4 hours
4 - 8 hours
9 -12 hours
More than 12 hours
Don't know

Default next: 4a-15

(Added 13/04/2003 05:22:46 PM by lparkin Modified 13/04/2003 05:23:12 PM by lparkin)

Q15 Which class <>were you<><>was your <><> travelling in on this leg of <>your<><><>her<><>his<</Umale>><> journey? **Q15**

PROMPT IF NECESSARY: Was it first class, business class, economy class, or some other class?

Response type: Single select from

First
Business
Economy
Other
Don't know

Default next: 4a-16

(Added 13/04/2003 05:15:49 PM by lparkin Modified 15/04/2003 10:06:12 AM by lparkin)

Q16 Did <>you<><>your <><> have a seat on the aisle on this leg of <>your<><><>her<><>his<</Umale >><> journey? **Q16**

Response type: Single select from
Yes
No
Don't know

Default next: 4a-17

(Added 13/04/2003 05:17:09 PM by lparkin Modified 15/04/2003 01:47:18 PM by lparkin)

Q17 Did <>you<><>your<><> take any sleeping pills immediately before, or during, this leg of <>your<><><>her<><>his<</Umale><><> journey? **Q17**

Response type: Single select from
Yes
No
Don't know

Default next: 4a-18

(Added 13/04/2003 05:17:51 PM by lparkin Modified 15/04/2003 10:06:50 AM by lparkin)

Q18 How long did <>you<><>your <><> spend at the _____ airport (airport at which landed at end of this leg of journey)? **Q18**
(record hours, or minutes, or "-2" if don't know)

Response type: Text entry with input mask
xx.xhrs(xxm)

Post-logic: alltrim(QData4a.q18) ="-2" GOTO:4a19

Default next: 4a-20

(Added 11/03/2003 10:22:44 AM by lparkin Modified 20/05/2003 11:20:46 AM by lianne parkin)

Q19 Do you think it would have been less than 2 hours, between 2 - 4 hours, between 5 to 8 hours, between 9 to 12 hours, or more than 12 hours? **Q19**

Response type: Single select from
Less than 2 hours
2 - 4 hours
5 - 8 hours
9 - 12 hours
More than 12 hours
Don't know

Default next: 4a-20

(Added 11/03/2003 10:37:42 AM by lparkin Modified 14/04/2003 08:58:13 PM by lparkin)

Q20 Did <>your<><>your<>'s<> aeroplane land anywhere else before it reached _____ airport (final destination)? **Q20**

Response type: Single select from
Yes
No
Don't know

Response logic:
4a12

Default next: 4a-21 End of Loop

(Added 11/04/2003 05:31:15 PM by lparkin Modified 13/04/2003 06:41:24 PM by lparkin)

Q21 How long was the flight between _____ (airport from which departed on this leg of journey) and _____(final destination)? **Q21**
(record hours, or minutes, or "-2" if don't know)

Response type: Text entry with input mask

xx.xhrs(xxm)

Post-logic: alltrim(QData4a.q21)="-2" GOTO:4a22

Default next: 4a-23

(Added 13/04/2003 06:12:22 PM by lparkin Modified 20/05/2003 11:21:13 AM by lianne parkin)

Q22 Do you think it would have been less than 4 hours, between 4 to 8 hours, between 9 to 12 hours, or more than 12 hours? **Q22**

Response type: Single select from

Less than 4 hours
4 - 8 hours
9 -12 hours
More than 12 hours
Don't know

Default next: 4a-23

(Added 13/04/2003 06:12:48 PM by lparkin Modified 13/04/2003 06:13:14 PM by lparkin)

Q23 Which class <>were you<><>was your <><> travelling in on this leg of <>your<><><>her<><>his<</Umale>><> journey? **Q23**

PROMPT IF NECESSARY: Was it first class, business class, economy class, or some other class?

Response type: Single select from

First
Business
Economy
Other
Don't know

Default next: 4a-24

(Added 13/04/2003 06:13:54 PM by lparkin Modified 15/04/2003 10:07:10 AM by lparkin)

Q24 Did <>you<><>your <><> have a seat onthe aisle on this leg of<>your<><><>her<><>his<</Umale>><> journey? **Q24**

Response type: Single select from

Yes
No
Don't know

Default next: 4a-25

(Added 13/04/2003 06:14:48 PM by lparkin Modified 15/04/2003 10:07:19 AM by lparkin)

Q25 Did <>you<><>your<><> take any sleepingpills immediately before, or during, this leg of <>your<><><>her<><>his<</Umale>><> journey? **Q25**

Response type: Single select from

Yes
No
Don't know

Default next: 4a-26

(Added 13/04/2003 06:15:27 PM by lparkin Modified 15/04/2003 10:07:31 AM by lparkin)

Q26 Did <>you<><>your <><> go on any domestic flights within New Zealand, or another country, DIRECTLY BEFORE the international flight? **Q26**

First international flight during the four weeks before the index date — Section 4a

Response type: Single select from

Yes
No
Don't know

Response logic:
4a27

Default next: 4a-29

(Added 14/03/2003 10:10:28 AM by lparkin Modified 13/04/2003 06:41:38 PM by lparkin)

Q27 From which airport(s) did the domestic flight(s) depart? (record name(s) of airport(s) / don't know) **Q27**

Response type: Single line text

200

Default next: 4a-28

(Added 11/03/2003 11:27:01 AM by lparkin Modified 13/04/2003 06:10:45 PM by lparkin)

Q28 On what date(s) did <>you<><>your <><> depart from this airport(s)? (record dd/mm/yy [local time] / don't know) **Q28**

Response type: Single line text

200

Default next: 4a-29

(Added 11/03/2003 11:29:20 AM by lparkin Modified 13/04/2003 06:10:23 PM by lparkin)

Q29 Did <>you<><>your <><> go on any domestic flights within New Zealand, or another country, DIRECTLY AFTER the international flight? **Q29**

Response type: Single select from

Yes
No
Don't know

Response logic:
4a30

Default next: 4a-32

(Added 11/03/2003 11:21:36 AM by lparkin Modified 13/04/2003 06:08:53 PM by lparkin)

Q30 At which airport(s) did the domestic flight(s) arrive? (record name(s) of airport(s) / don't know) **Q30**

Response type: Single line text

200

Default next: 4a-31

(Added 13/04/2003 05:32:13 PM by lparkin Modified 13/04/2003 06:08:20 PM by lparkin)

Q31 On what date(s) did <>you<><>your <><> arrive at this airport(s)? (record dd/mm/yy [local time] / don't know) **Q31**

Response type: Single line text

200

Default next: 4a-32

(Added 13/04/2003 03:55:16 PM by lparkin Modified 13/04/2003 06:09:19 PM by lparkin)

Q32 Did <>you<><>your <><> go on any other international flights during the four weeks between the <> and the <>? **Q32**

Response type: Single select from

Yes
No
Don't know

Post-logic: QData4a.q32=1 GOTO:4b01

Default next: 9a-00a

(Added 11/03/2003 11:32:24 AM by lparkin Modified 16/04/2003 07:31:39 PM by lianne parkin)

First domestic flight within another country in the four weeks before the index date

Q00a Now I would like to ask you some questions about any domestic flights that <>you<><>your <><> might have taken WITHIN a country OTHER THAN New Zealand in the four weeks between the <> and the <>. **Q00a**

Pre-logic: Qdata4a.q01=1 GOTO:9a00b
Response type: Statement
Default next: 9a-01

(Added 13/03/2003 03:42:16 PM by lparkin Modified 11/05/2003 07:22:25 PM by lianne parkin)

Q00b Now I would like to ask you some questions about any domestic flights that <>you<><>your <><> might have taken WITHIN a country OTHER THAN New Zealand in the four weeks between the <> and the <>. **Q00b**

I would like to know about all your <><>'s<> domestic flights within another country, not just the ones that <>you<><><>s<><>he<> <> might have been on directly before, or after, an international flight.

Response type: Statement
Default next: 9a-01

(Added 13/03/2003 03:51:10 PM by lparkin Modified 11/05/2003 06:37:41 PM by lianne parkin)

Q01 Did <>you<><>your <><> go on any domestic flights WITHIN a country OTHER THAN New Zealand between the <> and the <>? **Q01**

Response type: Single select from
Yes
No
Don't know

Response logic:
9a02

Default next: 10-00

(Added 13/03/2003 03:44:43 PM by lparkin Modified 11/05/2003 04:05:25 PM by lianne parkin)

Q02 From which airport did <>your<><>your <>'s<> flight depart? **Q02**
(record name of airport / don't know)

IF MORE THAN ONE FLIGHT DURING FOUR WEEK PERIOD: I am going to ask you some questions about each flight.

Lets take the first flight that <>you<><>your <><> had between the <> and the <>.

Response type: Single line text
200
Default next: 9a-03

(Added 13/03/2003 03:59:40 PM by lparkin Modified 15/04/2003 04:56:39 PM by lianne parkin)

Q03 On what date did <>you<><>your <><> depart from this airport? **Q03**
(record dd/mm/yy [local time] / don't know)

Response type: Single line text
200
Default next: 9a-04

(Added 13/03/2003 04:00:56 PM by lparkin Modified 15/04/2003 10:44:00 AM by lparkin)

Q04 At which airport did <>your<><>your <>'s<> flight arrive? **Q04**
(record name of airport / don't know)

First domestic flight within another country in the four weeks before the

Response type: Single line text

200

Default next: 9a-05

(Added 13/03/2003 04:21:55 PM by lparkin Modified 15/04/2003 10:12:24 AM by lparkin)

Q05 On what date did <>you<><>your <><> arrive at this airport? (record dd/mm/yy [local time] / don't know) **Q05**

Response type: Single line text

200

Default next: 9a-06

(Added 13/03/2003 04:23:33 PM by lparkin Modified 14/04/2003 08:11:14 PM by lparkin)

Q06 Did the aeroplane land anywhere between _____(airport where began journey) and _____(final destination)? **Q06**

Response type: Single select from

Yes
No
Don't know

Response logic:

9a12

Default next: 9a-07

(Added 13/03/2003 04:29:48 PM by lparkin Modified 14/04/2003 08:11:58 PM by lparkin)

Q07 How long was the flight between _____(airport where began journey) and _____(final destination)? (record hours, or minutes, or "-2" if don't know) **Q07**

Response type: Text entry with input mask

xx.xhrs(xxm)

Post-logic: alltrim(QData9a.q07)="-2" GOTO:9a08

Default next: 9a-09

(Added 13/03/2003 05:28:14 PM by lparkin Modified 20/05/2003 12:05:05 PM by lianne parkin)

Q08 Do you think it would have been less than 2 hours, between 2 - 4 hours, between 5 to 8 hours, between 9 to 12 hours, or more than 12 hours? **Q08**

Response type: Single select from

Less than 2 hours
2 - 4 hours
5 - 8 hours
9 -12 hours
More than 12 hours
Don't know

Default next: 9a-09

(Added 13/03/2003 05:30:38 PM by lparkin Modified 14/04/2003 08:59:42 PM by lparkin)

Q09 Which class <>were you<><>was your <><> travelling in? **Q09**

PROMPT IF NECESSARY: Was it first class, business class, economy class, or some other class?

Response type: Single select from

First class
Business class
Economy class
Other
Don't know

Default next: 9a-10

(Added 13/03/2003 04:25:07 PM by lparkin Modified 14/04/2003 08:50:55 PM by lparkin)

First domestic flight within another country in the four weeks before the

Q10 Did <>you<><>your <><> have a seat on the aisle? **Q10**

Response type: Single select from
Yes
No
Don't know

Default next: 9a-11

(Added 13/03/2003 04:27:11 PM by lparkin Modified 14/04/2003 08:15:58 PM by lparkin)

Q11 Did <>you<><>your <><> take any sleeping pills immediately before, or during, the flight? **Q11**

Response type: Single select from
Yes
No
Don't know

Default next: 9a-26

(Added 13/03/2003 04:24:42 PM by lparkin Modified 14/04/2003 08:50:26 PM by lparkin)

Q12 Where did the aeroplane land? **Q12**
(record name of airport / don't know)

Response type: Single line text
200

Default next: 9a-13 Start of Loop

(Added 13/03/2003 04:30:29 PM by lparkin Modified 14/04/2003 08:16:27 PM by lparkin)

Q13 How long was the flight between _____ (airport from which departed on this leg of journey) and _____ (airport at which arrived on this leg of journey)? **Q13**
(record hours, or minutes, or "-2" if don't know)

Response type: Text entry with input mask
xx.xhrs(xxm)

Post-logic: alltrim(QData9a.q13)="-2" GOTO:9a14

Default next: 9a-15

(Added 14/04/2003 08:18:22 PM by lparkin Modified 20/05/2003 12:05:30 PM by lianne parkin)

Q14 Do you think it would have been less than 2 hours, between 2 - 4 hours, between 5 to 8 hours, between 9 to 12 hours, or more than 12 hours? **Q14**

Response type: Single select from
Less than 2 hours
2 - 4 hours
5 - 8 hours
9 -12 hours
More than 12 hours
Don't know

Default next: 9a-15

(Added 14/04/2003 08:19:14 PM by lparkin Modified 14/04/2003 08:59:26 PM by lparkin)

Q15 Which class <>were you<><>was your <><> travelling in on this leg of <>your<><><>her<><>his<</Umale>><> journey? **Q15**

PROMPT IF NECESSARY: Was it first class, business class, economy class, or some other class?

First domestic flight within another country in the four weeks before the

Response type: Single select from

First class
Business class
Economy class
Other
Don't know

Default next: 9a-16

(Added 14/04/2003 08:24:53 PM by lparkin Modified 15/04/2003 10:16:40 AM by lparkin)

Q16 Did <>you<><>your <><> have a seat on the aisle on this leg of<>your<><><>her<><>his<</Umale>> <> journey? **Q16**

Response type: Single select from

Yes
No
Don't know

Default next: 9a-17

(Added 14/04/2003 08:25:58 PM by lparkin Modified 15/04/2003 10:16:49 AM by lparkin)

Q17 Did <>you<><>your <><> take any sleeping pills immediately before, or during, the flight on this leg of <>your<><><>her<><>his<</Umale>><> journey? **Q17**

Response type: Single select from

Yes
No
Don't know

Default next: 9a-18

(Added 14/04/2003 08:27:17 PM by lparkin Modified 15/04/2003 10:16:58 AM by lparkin)

Q18 How long did <>you<><>your <><> spend at the _____ airport (airport at which landed at end of this leg of journey)? **Q18**
(record hours, or minutes, or "-2" if don't know)

Response type: Text entry with input mask

xx.xhrs(xxm)

Post-logic: alltrim(QData9a.q18)="-2" GOTO:9a19

Default next: 9a-20

(Added 13/03/2003 04:31:59 PM by lparkin Modified 20/05/2003 12:05:51 PM by lianne parkin)

Q19 Do you think it would have been less than 2 hours, between 2 - 4 hours, between 5 to 8 hours, between 9 to 12 hours, or more than 12 hours? **Q19**

Response type: Single select from

Less than 2 hours
2 - 4 hours
5 - 8 hours
9 -12 hours
More than 12 hours
Don't know

Default next: 9a-20

(Added 13/03/2003 04:32:19 PM by lparkin Modified 14/04/2003 08:59:11 PM by lparkin)

Q20 Did <>your<><>your <>'s<> aeroplane land anywhere else before it reached _____ airport (final destination)? **Q20**

First domestic flight within another country in the four weeks before the

Response type: Single select from

Yes
No
Don't know

Response logic:
9a12

Default next: 9a-21 End of Loop

(Added 14/04/2003 08:38:55 PM by lparkin Modified 15/04/2003 10:44:35 AM by lparkin)

Q21 How long was the flight between _____ (airport from which departed on this leg of journey) and _____ (final destination)?
(record hours, or minutes, or "-2" if don't know) **Q21**

Response type: Text entry with input mask

xx.xhrs(xxm)

Post-logic: alltrim(QData9a.q21)="-2" GOTO:9a22

Default next: 9a-23

(Added 14/04/2003 08:39:40 PM by lparkin Modified 20/05/2003 12:06:11 PM by lianne parkin)

Q22 Do you think it would have been less than 2 hours, between 2 - 4 hours, between 5 to 8 hours, between 9 to 12 hours, or more than 12 hours? **Q22**

Response type: Single select from

Less than 2 hours
2 - 4 hours
5 - 8 hours
9 -12 hours
More than 12 hours
Don't know

Default next: 9a-23

(Added 14/04/2003 08:40:46 PM by lparkin Modified 14/04/2003 08:58:59 PM by lparkin)

Q23 Which class <>were you<><>was your <><> travelling in on this leg of <>your<><><>her<><>his<</Umale>><> journey? **Q23**

PROMPT IF NECESSARY: Was it first class, business class, economy class, or some other class?

Response type: Single select from

First class
Business class
Economy class
Other
Don't know

Default next: 9a-24

(Added 14/04/2003 08:42:09 PM by lparkin Modified 15/04/2003 10:17:33 AM by lparkin)

Q24 Did <>you<><>your <><> have a seat onthe aisle on this leg of<>your<><><>her<><>his<</Umale>><> journey? **Q24**

Response type: Single select from

Yes
No
Don't know

Default next: 9a-25

(Added 14/04/2003 08:43:18 PM by lparkin Modified 15/04/2003 10:17:43 AM by lparkin)

Q25 Did <>you<><>your <><> take any sleeping pills immediately before, or during, the flight on this leg of <>your<><><>her<><>his<</Umale **Q25**

First domestic flight within another country in the four weeks before the

>><> journey?

Response type: Single select from

Yes
No
Don't know

Default next: 9a-26

(Added 14/04/2003 08:43:47 PM by lparkin Modified 15/04/2003 10:17:57 AM by lparkin)

Q26 Did <>you<><>your <><> go on any other flights WITHIN a country OTHER THAN New Zealand during the four weeks between the <> and the <>? **Q26**

Response type: Single select from

Yes
No
Don't know

Response logic:

Post-logic: Qdata9a.q26=1 GOTO:9b01

Default next: 10-00

(Added 14/04/2003 08:45:13 PM by lparkin Modified 11/05/2003 04:05:34 PM by lianne parkin)

Other travel in the four weeks before the index date

Q00 Now I would like to ask you some questions about any other travel that <>your <><> might have done in the four weeks between the <> and the <>. **Q00**

I realise that it may be difficult to remember, just do the best you can.

Pre-logic: Reference.ucontrol GOTO:5 00
Response type: Statement
Default next: 10-01

(Added 13/03/2003 03:42:16 PM by lparkin Modified 11/05/2003 07:39:22 PM by lianne parkin)

Q01 Did <>your <><> go on any long journeys (by car, bus, train, or some other form of transport) that took at least four hours in the four weeks between the <> and the <>? (record details, including dates, mode of transport, and duration of journey[s]) **Q01**

Response type: Edit box (open ended) **Response logic:**
Default next: 5 -00

(Added 13/03/2003 03:44:43 PM by lparkin Modified 14/05/2003 09:51:45 PM by lianne parkin)

Q00 I now have a few questions about <>your<><>your <>'s<> height and weight in the past. **Q00**

I realise that it can be difficult to give exact answers to these sorts of questions. Just do the best that you can.

Response type: Statement

Default next: 5 -01a

(Added 11/03/2003 02:09:58 PM by lparkin Modified 16/04/2003 09:00:17 PM by lianne parkin)

Q01a How tall do you think <>you were<><>your <> was<> on the <>? **Q01a**
(record height [feet and inches or metres] / or "-2" if don't know)
PROMPT IF NECESSARY: You can answer in feet and inches, or in metres and centimetres

(Further prompt for next of kin): It might be helpful to think about how tall you are, and then how tall <> was in relation to you.

Response type: Text entry with input mask

#.##m#(#ft##")

Post-logic: alltrim(Qdata5.q01a) ="-2" GOTO:5 01b

Default next: 5 -02a

(Added 11/03/2003 01:43:05 PM by lparkin Modified 27/05/2003 03:54:14 PM by lianne parkin)

Q01b <>Were you<><>Was <>s<>he<> of average height, above average height, or below average height? **Q01b**

Response type: Single select from

Average
Above average
Below average
Don't know

Default next: 5 -01c

(Added 11/03/2003 01:49:32 PM by lparkin Modified 20/03/2003 12:04:20 PM by lparkin)

Q01c (Record any other comments about height) **Q01c**

Response type: Single line text

200

Default next: 5 -02a

(Added / / : : AM by Modified / / : : AM by)

Q02a What do you think <>you<><>your <><> would have weighed when <>you were<><><>s<>he was<> 20 years old? **Q02a**
(record weight [stones and pounds or kilograms] / or "-2" if don't know)

Pre-logic: (Reference.ucontrol and Reference.age<=20) or (!Reference.ucontrol and Reference.uage<=20) GOTO:5 03a

Response type: Text entry with input mask

###.#kg#(##st###pds)

Post-logic: alltrim(Qdata5.q02a) ="-2" GOTO:5 02b

Default next: 5 -03a

(Added 11/03/2003 01:51:08 PM by lparkin Modified 20/05/2003 12:32:06 PM by lianne parkin)

Q02b Do you think <>your<><><>her<><>his<</Umale >><> weight would have been about average, more than average, or less than average? **Q02b**

Response type: Single select from

Average
More than average
Less than average
Don't know

Default next: 5 -02c

(Added 11/03/2003 01:59:30 PM by lparkin Modified 15/05/2003 03:47:11 PM by lianne parkin)

Q02c (Record any other comments about weight) **Q02c**

Response type: Single line text

200

Default next: 5 -03a

(Added / / : : AM by Modified / / : : AM by)

Q03a What do you think <>you<><>your <><> would have weighed on the <>?
(record weight [stones and pounds or kilograms] / or "-2" if don't know) **Q03a**

Response type: Text entry with input mask

###.#kg#(##st###pds)

Post-logic: alltrim(Qdata5.q03a) ="-2" GOTO:5 03b

Default next: 5 -04a

(Added 11/03/2003 02:01:43 PM by lparkin Modified 20/05/2003 12:32:27 PM by lianne parkin)

Q03b Do you think <>your<><><>her<><>his<</Umale >><> weight would have been about average, more than average, or less than average? **Q03b**

Response type: Single select from

Average
More than average
Less than average
Don't know

Default next: 5 -03c

(Added 11/03/2003 02:03:10 PM by lparkin Modified 16/04/2003 10:50:26 AM by lianne parkin)

Q03c (Record any other comments about weight) **Q03c**

Response type: Single line text

200

Default next: 5 -04a

(Added 16/04/2003 10:50:35 AM by lianne parkin Modified / / : : AM by)

Q04a I have one last question about weight and height. For <>your<> <><>her<><>his<><> height, <>were you<><>was your <><> about the right weight, overweight, or underweight on the <>? **Q04a**

Response type: Single select from

About right
Overweight
Underweight
Don't know

Default next: 5 -04b

(Added 11/03/2003 02:07:25 PM by lparkin Modified 16/04/2003 10:44:05 AM by lianne parkin)

Q04b (Record any other comments about weight in relation to height) **Q04b**

Height and weight

Response type: Single line text

200

Default next: 6 -00

(Added / / : : AM by Modified / / : : AM by)

Q00 Now I would like to ask you a few questions about the medical history of <>your<><>your <>'s<> family before the <>. **Q00**

I realise that you won't necessarily know a lot about the medical history of <>your<><>your <>'s<> family. Just answer the questions as best as you can.

So, before the <>:

Response type: Statement

Default next: 6 -01a

(Added 19/03/2003 10:18:20 AM by lparkin Modified 16/04/2003 09:01:00 PM by lianne parkin)

Q01a As far as you know, was anyone in <>your<><>your <>'s<> immediate, or extended, family (and by extended family I mean grandparents, aunts, cousins, nieces etc) ever treated for deep vein thrombosis? **Q01a**

PROMPT IF NECESSARY: This is a condition where blood clots have formed in the deep veins of the legs or pelvis

Response type: Single select from

Yes
No
Don't know

Response logic:

6 01b

Default next: 6 -02a

(Added 11/03/2003 02:15:30 PM by lparkin Modified 19/03/2003 10:20:23 AM by lparkin)

Q01b What relationship was this person / were these people to <>you<><> to your <><>? **Q01b**

(NB. (i) Record only biological relatives
(ii) For aunts, uncles, cousins, grandparents, and great-grandparents, record whether maternal, paternal, or unknown
(iii) Record the number of relatives who had a DVT. For example: 3 maternal aunts)

IF AN UNCLE OR AUNT IS IDENTIFIED, ASK: Is this a direct relative, or are they related to <>you<><>your <><> through marriage?

ALSO ASK: Did <>you<><>your <><> have any other relatives who were treated for deep vein thrombosis?

Response type: Single line text

200

Default next: 6 -02a

(Added 11/03/2003 02:22:58 PM by lparkin Modified 11/05/2003 07:12:19 PM by lianne parkin)

Q02a As far as you know, was anyone in <>your<><>your <>'s<> immediate, or extended, family ever treated for pulmonary embolism? **Q02a**

PROMPT IF NECESSARY: This is the condition where blood clots in the legs or pelvis break off and travel up to the arteries of the lungs.

Response type: Single select from

Yes
No
Don't know

Response logic:

6 02b

Default next: 7 -00

(Added 11/03/2003 02:27:37 PM by lparkin Modified 19/03/2003 10:36:27 AM by lparkin)

Q02b What relationship was this person / were these people to <>you<><>to your <><>? **Q02b**

(NB. (i) Record only biological relatives

(ii) For aunts, uncles, cousins, grandparents, and great-grandparents, record whether maternal, paternal, or unknown
(iii) Record the number of relatives who had pulmonary embolism. For example: 3 maternal aunts)

IF AN UNCLE OR AUNT IS IDENTIFIED, ASK: Is this a direct relative, or are they related to <>you<><>your <><> through marriage?

ALSO ASK: Did <>you<><>your <><> have any other relatives who were treated for deep vein thrombosis?

Response type: Single line text

200

Default next: 7 -00

(Added 11/03/2003 02:27:55 PM by lparkin Modified 11/05/2003 07:12:56 PM by lianne parkin)

Q00 Finally I would like to ask you some general questions about <>yourself<><>your <><>. **Q00**

The reason for asking these questions is that people's health can sometimes be affected by their personal circumstances.

The first questions are about education.

Response type: Statement

Default next: 7 -01

(Added 11/03/2003 06:57:59 PM by lparkin Modified 27/05/2003 08:55:33 PM by lianne parkin)

Q01 How many years did <>you<><>your <><> spend at secondary school (high school, technical school) before <>? **Q01**
(record country and number of years, or don't know)

PROMPT IF NECESSARY: The maximum time that people usually spend at secondary school in New Zealand is 5 years.

Response type: Single line text

200

Default next: 7 -02a

(Added 11/03/2003 02:37:34 PM by lparkin Modified 19/05/2003 11:23:02 AM by lianne parkin)

Q02a Before the <> did <>you<><>your <><> get any qualifications after <>you<><><>s<>he<> had left school? **Q02a**

(PROMPT IF NECESSARY By qualifications I mean degrees, diplomas, certificates, and the completion of apprenticeships)

Response type: Single select from **Response logic:**

Yes
No
Don't know
Still studying for qualification

Post-logic: Qdata7.q02a=1 or Qdata7.q02a=4 GOTO:7 02b

Default next: 7 -03a

(Added 11/03/2003 02:38:10 PM by lparkin Modified 22/05/2003 10:23:27 AM by lianne parkin)

Q02b What was <>your<><><>her<><>his<</Umale>><> highest qualification? **Q02b**

Response type: Single line text

200

Default next: 7 -03a

(Added 11/03/2003 02:44:26 PM by lparkin Modified 20/03/2003 12:11:18 PM by lparkin)

Q02c Classify the highest qualification **Q02c**

Pre-logic: lower(gcusername)<>"lianne parkin" GOTO:7 03a

Response type: Numeric

99

Default next: 7 -03a

(Added 11/03/2003 02:47:01 PM by lparkin Modified 11/05/2003 02:29:00 PM by lianne parkin)

Q03a The next question is about PAID employment. Did <>you<><>your<><> have a job on the <>? **Q03a**

Response type: Single select from

Yes
No
Don't know
Spontaneously reported was retired

Response logic:
7 03b

Default next: 7 -03c

(Added 11/03/2003 02:48:29 PM by lparkin Modified 16/04/2003 09:03:23 PM by lianne parkin)

Q03b What was that job? **Q03b**

IF NAME OR TYPE OF WORKPLACE STATED, ASK: What sort of work did <>you<><>your <><> do there?

Response type: Single line text

200

Default next: 7 -03d

(Added 11/03/2003 02:51:23 PM by lparkin Modified 19/03/2003 01:25:29 PM by lparkin)

Q03c What was the last job<>you<><><><>s<>he<> did before the <>? **Q03c**

IF NAME OR TYPE OF WORKPLACE STATED, ASK: What sort of work did <>you<><>your <><> do there?

Response type: Single line text

200

Default next: 7 -03d

(Added 11/03/2003 03:16:14 PM by lparkin Modified 13/05/2003 09:26:58 PM by lianne parkin)

Q03d What is the NZSEI code for that type of work? **Q03d**

Pre-logic: lower(gcusername)<>"lianne parkin" GOTO:7 04a

Response type: Numeric

999

Default next: 7 -04a

(Added 11/03/2003 03:21:57 PM by lparkin Modified 11/05/2003 07:13:38 PM by lianne parkin)

Q04a Did <>you<><>your <><> live with <>a spouse or partner<><>you / a spouse or partner<> on the <>? **Q04a**

Response type: Single select from

Yes
No
Don't know

Response logic:
7 04b

Default next: 7 -05a

(Added 11/03/2003 03:24:37 PM by lparkin Modified 27/05/2003 03:33:11 PM by lianne parkin)

Q04b Did <>your spouse or partner<><>you<> have a job on that date? **Q04b**

Response type: Single select from

Yes
No
Don't know
Spontaneously reported was retired

Response logic:
7 04c

Default next: 7 -04d

(Added 11/03/2003 03:27:14 PM by lparkin Modified 11/05/2003 03:15:27 PM by lianne parkin)

Q04c What was that job? **Q04c**

IF NAME OR TYPE OF WORKPLACE STATED, ASK: What sort of work did <>your spouse or partner<><>you<> do there?

Response type: Single line text

200

Default next: 7 -04e

(Added 11/03/2003 03:27:47 PM by lparkin Modified 11/05/2003 03:19:49 PM by lianne parkin)

Q04d What was the last job <>your spouse or partner<><>you<> did before the <>? **Q04d**

IF NAME OR TYPE OF WORKPLACE STATED, ASK: What sort of work did<>your spouse or partner<><>you<> do there?

Response type: Single line text

200

Default next: 7 -04e

(Added 11/03/2003 03:31:31 PM by lparkin Modified 11/05/2003 03:19:55 PM by lianne parkin)

Q04e What is the NZSEI code for that type of work? **Q04e**

Pre-logic: lower(gcusername)<>"lianne parkin" GOTO:7 05a

Response type: Numeric

999

Default next: 7 -05a

(Added 11/03/2003 03:33:44 PM by lparkin Modified 11/05/2003 07:13:53 PM by lianne parkin)

Q05a Now I'd like to ask you a question about ethnicity. Which ethnic group <>do you<><>did your <><> belong to? **Q05a**

(read out if necessary and select as many as apply)

Response type: Multichoice from **Response logic:**

New Zealand European
New Zealand Maori
Samoan
Cook Island Maori
Tongan
Niuean
Chinese
Indian
Other European (specify on next page)
Other non-European (specify on next page

Post-logic: bittest(Qdata7.q05a,9) or bittest(Qdata7.q05a,10) GOTO:7 05b

Default next: 7 -05c

(Added 11/03/2003 03:35:00 PM by lparkin Modified 16/05/2003 02:01:20 PM by lianne parkin)

Q05b (If classified as "Other European" or "Other", specify ethnicity) **Q05b**

Response type: Single line text

200

Default next: 7 -05c

(Added 11/05/2003 02:42:06 PM by lianne parkin Modified / / : : AM by)

Q05c One of the risk factors for the condition we are studying is more common among people who have SOME ancestors who were European. So I would like to ask you a question about the ethnicity of your<> <>'s<> ancestors. **Q05c**

Were either of your<> <>'s<> parents, or any of <>your<><><>her<><>his<</Umale>><> grandparents, great-grandparents, or other ancestors, of European descent?

Pre-logic: bittest(Qdata7.q05a,1) or bittest(Qdata7.q05a,9) GOTO:8 00

Response type: Single select from

Yes
No
Don't know

Response logic:

7 05d

Default next: 8 -00

(Added 11/03/2003 03:40:18 PM by lparkin Modified 28/05/2003 12:33:52 PM by cblakey)

Q05d What relationship were they to <>you<><>your <><>? **Q05d**

(For grandparents and great-grandparents, record whether maternal or paternal)

Response type: Single line text

200

Default next: 8 -00

(Added 11/03/2003 03:46:59 PM by lparkin Modified 11/05/2003 02:39:35 PM by lianne parkin)

Q00 We have almost come to the end of the interview. **Q00**

Response type: Statement

Default next: 8 -01

(Added 11/03/2003 04:22:11 PM by lparkin Modified / / : : AM by)

Q01 I just want to confirm where you were on a particular date. Were you in New Zealand or temporarily overseas (for example on a holiday or a work-related trip) on the <>? **Q01**

Pre-logic: !Reference.ucontrol GOTO:8 04

Response type: Single select from

In New Zeland
Overseas
Don't know

Default next: 8 -02

(Added 11/03/2003 04:07:57 PM by lparkin Modified 11/05/2003 02:31:04 PM by lianne parkin)

Q02 I also want to confirm where you were on another date. Were you in New Zealand or temporarily overseas on the <>? **Q02**

Pre-logic: Reference.uindexdate=Reference.udod GOTO:8 03

Response type: Single select from

In New Zealand
Overseas
Don't know

Default next: 8 -03

(Added 11/03/2003 04:10:04 PM by lparkin Modified 24/03/2003 10:44:55 AM by lparkin)

Q03 Would you be willing to give your consent for us to confirm the dates of any hospital admissions you have had? We can do this without looking at your medical records. **Q03**

(PROMPT IF NECESSARY: Public and private hospitals use a confidential computer system to record the dates that people were admitted to hospital)

Response type: Password

Default next: 8 -04

(Added 11/03/2003 04:13:23 PM by lparkin Modified 13/05/2003 09:50:45 PM by lianne parkin)

Q04 If we needed to obtain further information for our research, may we write to you again? **Q04**

Response type: Password

Default next: 8 -05

(Added 11/03/2003 04:15:33 PM by lparkin Modified 12/05/2003 01:24:58 PM by lianne parkin)

Q05 Would you like to be sent a summary of the results of this study when it is completed? **Q05**

Response type: Single select from

Yes
No

Default next: 8 -06

(Added 11/03/2003 04:16:06 PM by lparkin Modified / / : : AM by)

Q06 Is there anything you wish to ask me, or any comments you would like to make? **Q06**

Response type: Edit box (open ended)

Default next: 8 -07

(Added 11/03/2003 04:16:47 PM by lparkin Modified 16/04/2003 09:07:09 PM by lianne parkin)

Q07 That is all the questions I had to ask you. Thank you very much for all your help. **Q07**

Response type: Statement

Default next: 8 -10

(Added 11/03/2003 04:17:23 PM by lparkin Modified 15/04/2003 05:00:13 PM by lianne parkin)

Q08 Record information about other international flights (if more than 15) **Q08**

(Record departure and destination airports, dates of departure and arrival, whether plane landed anywhere, time spent at airport, duration of flight(s), class of travel, aisle seat, use of sleeping pills, and whether any domestic flights before or after international flight)

Response type: Edit box (open ended)

Default next: 9a-00a

(Added 15/04/2003 04:58:46 PM by lianne parkin Modified 13/05/2003 09:47:58 PM by lianne parkin)

Q09 Record information about domestic flights within a country other than New Zealand (if more than 15) **Q09**

(Record departure and destination airports, dates of departure and arrival, whether plane landed anywhere, time spent at airport, duration of flight(s), class of travel, aisle seat, and use of sleeping

Response type: Edit box (open ended)

Default next: 5 -00

(Added 15/04/2003 05:01:11 PM by lianne parkin Modified 13/05/2003 09:48:24 PM by lianne parkin)

Q10 (Interviewer comments) **Q10**

Response type: Edit box (open ended)

Default next: 8 -11

(Added 11/03/2003 04:20:01 PM by lparkin Modified 12/05/2003 01:25:39 PM by lianne parkin)

Q11 (Name and signature of interviewer) **Q11**

Response type: Password

Default next: 99-9999

(Added 11/03/2003 04:19:30 PM by lparkin Modified 15/04/2003 05:01:23 PM by lianne parkin)

APPENDIX F: PUBLICATIONS ARISING FROM THE RESEARCH

Research letters

Oral contraceptives and fatal pulmonary embolism

Lianne Parkin, David C G Skegg, Meg Wilson, G Peter Herbison, Charlotte Paul

See Commentary page 2088

In a national case-control study of fatal pulmonary embolism in New Zealand women of childbearing age, we estimated that current users of combined oral contraceptives had a relative risk of 9·6 (95% CI 3·1–29·1). From national distribution data, the absolute risk of death from pulmonary embolism in current users was estimated to be 10·5 per million woman-years.

Since nearly all studies showing associations between oral contraception and venous thromboembolism (VTE) have involved non-fatal events, the possibility of referral or diagnostic bias has been suggested.[1] Such bias is unlikely in a study of fatal cases, since most young women who die unexpectedly are referred for necropsy. We studied fatal pulmonary embolism among all New Zealand women aged 15–49 years. Cases were identified from deaths between January, 1990, and August, 1998, certified with the underlying cause as codes 415·1, 451, or 453, from the International Classification of Diseases, ninth revision. We obtained clinical details and the names of family physicians from coroners' and police reports and hospital records; if necessary, we also wrote to the next of kin to ask for the name of the family physician. Of 43 women identified, four had insufficient evidence for the diagnosis of pulmonary embolism, and three did not normally live in New Zealand.

For the 36 eligible women, we asked the family physicians if an investigator (LP) could examine the records of the case and four controls. Every family physician agreed, but for seven cases the records had been lost. For the remainder of cases, the diagnosis had been confirmed by necropsy in 26, by ventilation-perfusion scans and pulmonary angiography in two, or by two independent physicians using standard criteria in one.[2] The median age was 32 years. We used the date of onset of the fatal episode as an index date.

For each case we selected four controls from the same family physician's group practice who had the same year of birth as the case (except five controls who were each born in an adjacent year). The controls were selected randomly from an age-sex register in 27 practices (computerised in all except one), and in the other two practices by random selection of medical records. We excluded potential controls if they were not normally resident in New Zealand, or did not belong to the practice, on the index date. The cases and controls had been with the same practices for an average of 8·2 years and 8·0 years, respectively. We obtained information about medical and contraceptive histories from the group practice and any family-planning-clinic records, by the same approach for cases and controls.

Current use of oral contraceptives was defined as prescribed use at any time during the 3 months before the index date. We excluded women who had reached the menopause (one case, five controls) or who had a history of VTE (two further cases). 17 (65%) of 26 cases and 25 (23%) of 111 controls were current users of combined oral contraceptives (table). We calculated odds ratios and 95% CI for VTE, by use of unconditional logistic regression. We did not use matched analysis since unstable estimates were obtained because of sparse data.

If we took non-users of any combined oral contraceptive as the reference group, the odds ratio (adjusted for age, weight, and family physician's practice) for all current users was 9·6 (95% CI 3·1–29·1). If we omitted controls with excluded cases, the adjusted odds ratio increased slightly to 10·2. Two cases had other potential causes of VTE (long-term immobility or major surgery); neither was using oral contraceptives. When such cases and controls were excluded, the odds ratio increased to 11·7 (3·5–38·5).

The women who died while using oral contraceptives had a median age of 29. Only three cases were first-time users of any combined oral contraceptive (with durations of use 3 months, 18 months, and 40 months, respectively). Third-generation oral contraceptives, containing desogestrel (seven deaths) or gestodene (five), were the most commonly used by the cases. Two cases were using a contraceptive pill that contains cyproterone acetate and ethinyloestradiol, and the odds ratio for such women was 17·6 (2·7–113). A study by WHO also found a high odds ratio of 14·9 (3·7–59·4) for this product.[2]

Only six (35%) deaths among cases using oral contraceptives had been reported to the Centre for Adverse Reactions Monitoring (CARM). CARM had been notified of a further death from pulmonary embolism (confirmed by necropsy) in a woman taking a contraceptive containing desogestrel, which had been miscoded in national mortality data. Contraceptive-supply data provided by the Ministry of Health showed that there were up to 1 717 153 woman-years of use of combined oral contraceptives in New Zealand during the period of the study, during which 18 users died. Thus, the absolute risk of death from idiopathic pulmonary embolism in women taking combined oral contraceptives was estimated to be 10·5 (6·2–16·6) per million woman-years. This estimate is probably conservative, since family-physician records could not be found for several cases and we ignored deaths for which pulmonary embolism was not certified as the underlying cause.

This death rate was higher than expected because the annual incidence of VTE in oral-contraceptive users has been estimated at one or two per 10 000 women, with a case fatality rate of only 1–2%.[2] The high mortality in New Zealand may partly reflect the extensive use of third-generation oral contraceptives, which seem to carry a higher

Progestogen in combined oral contraceptive	Cases	Controls	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Non-user	9	86	1·0	1·0
Levonorgestrel	3	8	3·6 (0·88–15·0)	5·1 (1·2–21·4)
Desogestrel or gestodene	12	15	7·6 (2·8–20·9)	14·9 (3·5–64·3)
Cyproterone acetate	2	1	19·1 (1·6–232)	17·6 (2·7–113)
All types	17	25†	6·5 (2·6–16·1)	9·6 (3·1–29·1)

*Adjusted for age (by individual year), weight (four categories, including missing values), and clustered on practice.
†One control using combined oral contraceptive containing norethisterone.

Current use of combined oral contraceptives

risk of VTE than older contraceptives.[3] Another case-control study of oral contraceptives and fatal pulmonary embolism, which involved deaths in England and Wales between 1986 and 1988,[4] would have included few if any women using these preparations. A death rate of 14 per million woman-years (based on six deaths) can be derived from a later cohort study.[5] Deaths from pulmonary embolism are rare among users of oral contraceptives, but the absolute risks should not be thought of as "infinitesimal, of no clinical importance and definitely of no public health significance".[1]

This study was funded by the New Zealand Ministry of Health. We thank family physicians and the Family Planning Association for their assistance, and David Coulter and Janelle Ashton for information from CARM.

1 Spitzer WO. The aftermath of a pill scare: regression to reassurance. *Hum Reprod Update* 1999; 5: 736–45.
2 WHO Collaborative Study. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995; **346**: 1575–88.
3 Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1998; **57**: 169–81.
4 Thorogood M, Mann J, Murphy M, Vessey M. Risk factors for fatal venous thromboembolism in young women: a case-control study. *Int J Epidemiol* 1992; **21**: 48–52.
5 Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; **346**: 1589–93.

Department of Preventive and Social Medicine, University of Otago, PO Box 913, Dunedin, New Zealand (L Parkin MB, Prof D C G Skegg FRSNZ, M Wilson MHealSc, G P Herbison MSc, C Paul PhD)

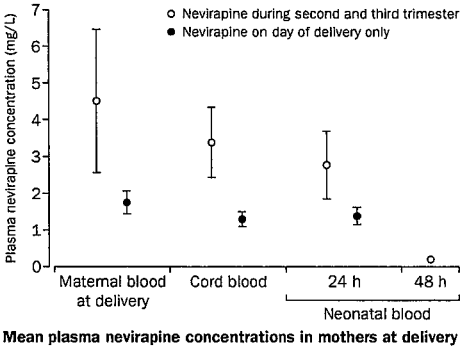
Correspondence to: Prof David Skegg

Pharmacological implications of lengthened in-utero exposure to nevirapine

G P Taylor, E G H Lyall, D Back, C Ward, G Tudor-Williams

Given as a single dose to the mother during labour, nevirapine can protect the neonate from HIV-1 infection for up to 7 days. However, after maternal nevirapine therapy during pregnancy, neonatal plasma concentrations of nevirapine decline more rapidly, suggesting in-utero liver enzyme induction.

Mother-to-child transmission of HIV-1 can be reduced to less than 2% by avoidance of breastfeeding, elective caesarean section, and perinatal zidovudine.[1] Also, when given as a single oral dose to the mother once labour has been established, nevirapine rapidly crosses the placenta and has a lengthened half-life in the neonate such that therapeutic plasma concentrations can be sustained for 7 days with only one additional oral dose given to the neonate after 48–72 h.[2] With this intervention, early peripartum transmission of HIV-1 can be reduced by 50% compared with zidovudine taken during the same period.[3] Current guidelines recommend that triple antiretroviral therapy rather than zidovudine monotherapy should be started during the second and third trimesters of pregnancy for women with symptomatic HIV-1 infection, high viral load, or low CD4-lymphocyte counts.[4] A regimen of nevirapine with two nucleoside analogue reverse-transcriptase inhibitors (NRTIs) is frequently prescribed because of its simplicity, tolerability, and efficacy. However, with the exception of zidovudine, didanosine, and, during the last 2 weeks of gestation, lamivudine, antiretroviral therapy pharmacokinetics during pregnancy have not been reported. We measured steady-state nevirapine plasma concentrations in women prescribed nevirapine (plus two NRTIs) during the second and third trimesters of pregnancy, and in their babies.



Mean plasma nevirapine concentrations in mothers at delivery in umbilical-cord blood, and in neonates at 24–48 h
Bars indicate SDs.

18 pregnant women (15 African, two white, and one Asian) were treated with nevirapine-containing regimens according to national guidelines.[4] For antiretroviral-naive mothers the combination of nevirapine, zidovudine, and lamivudine was commonly the first-line therapy. The therapy of mothers who conceived at the time of treatment was only changed in the case of viral failure or side-effects. For mothers previously exposed to antiretroviral therapy or for whom therapy had failed, new regimens were chosen after testing for genotypic resistance. The women were advised of the potential risks and benefits of therapy, and gave informed consent for therapeutic drug monitoring and for nevirapine concentration to be measured using the same blood sample taken for diagnostic HIV-1 DNA PCR. Nevirapine 200 mg daily was prescribed for the first 2 weeks, and thereafter 200 mg twice daily, with the regular doses taken on the day of delivery. Three mothers took their initial dose of nevirapine during labour or shortly before elective caesarean section. Whole blood was centrifuged after venesection and plasma stored at –20°C until analysis for nevirapine concentration by high-performance liquid chromatography.

Plasma nevirapine concentrations are shown in the figure. In the three mothers who started nevirapine on the day of delivery, mean neonatal nevirapine plasma concentrations at 24 h (1·39 mg/L) were 81% of maternal concentrations (1·71 mg/L), and 107% of cord concentrations (1·29 mg/L).

In the 15 mothers who were treated during pregnancy, the mean maternal plasma concentrations at the end of the first 4 weeks of therapy (4·62 mg/L) and at delivery (4·45 mg/L), were more than 400 times the reported median inhibitory concentration of nevirapine for wild-type HIV-1.[5] The mean concentration in cord blood (3·41 mg/L) was 76% of maternal nevirapine concentration at delivery ($p=0·03$, paired t test). 24 h after delivery the mean neonatal concentration (2·71 mg/L) was 60% of the maternal concentration at delivery ($p=0·01$). Because this suggested more rapid clearance of nevirapine than expected, venesection of one infant was deferred until 48 h after delivery. In this neonate the plasma nevirapine concentration (0·2 mg/L) was only 5% of the concentration in cord blood and 3% of the concentration in maternal blood.

Steady-state plasma nevirapine concentrations during the second and third trimesters of pregnancy were similar to published data for non-pregnant adults,[5] which suggests that the dose of nevirapine does not require adjustment in

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ORIGINAL REPORT

Psychotropic drugs and fatal pulmonary embolism

Lianne Parkin MB, DPH, David C. G. Skegg MB, DPhil*, G. Peter Herbison MSc and Charlotte Paul MB, PhD

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SUMMARY

Purpose To examine the association between the use of psychotropic drugs and fatal pulmonary embolism.
Methods We conducted a national case-control study of fatal pulmonary embolism. Cases were 75 New Zealand men and women aged 15–59 years who died between 1 January 1990 and 31 December 1998, where the underlying cause of death was certified as codes 415.1, 451 or 453 of the International Classification of Diseases (9th Revision). Four controls, matched for sex and age, were selected from the general practice to which each case had belonged. Information was abstracted from the records of general practitioners, family planning clinics and psychiatric services. Odds ratios and 95% confidence intervals (95% CI) were estimated using conditional logistic regression. The key analyses were restricted to cases ($n = 62$) and controls ($n = 243$) without major risk factors for venous thromboembolism.
Results Compared to non-use, the adjusted odds ratio for current use of antipsychotic drugs was 13.3 (95% CI: 2.3–76.3). Low potency antipsychotics appeared to carry the highest risk (odds ratio: 20.8 [95% CI: 1.7–259.0]). The main drug involved was thioridazine. The odds ratio for current use of antidepressants was also increased, at 4.9 (95% CI: 1.1–22.5).
Conclusions Our results for conventional antipsychotics are consistent with previous studies of non-fatal venous thromboembolism. The finding for antidepressants needs to be replicated in other studies. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — antipsychotics; antidepressants; psychotropics; venous thromboembolism; pulmonary embolism; case-control study

INTRODUCTION

In the year 2000, Zornberg and Jick reported that current users of antipsychotic drugs have an increased risk of non-fatal idiopathic venous thromboembolism.[1] Their study, based on the United Kingdom General Practice Research Database (GPRD), estimated the relative risk at 7.1 (95% CI: 2.3–21.9) for all antipsychotics and at 24.1 (95% CI: 3.3–172.7) for low potency preparations. Re-analysis of a case-control study of deep vein thrombosis provided support for the hypothesis that antipsychotic drugs may be a risk factor for this condition.[2]

The only study to examine formally the risk of fatal venous thromboembolic events in users of antipsychotics was confined to an atypical preparation (clozapine).[3] We expanded a national case-control study of fatal pulmonary embolism[4] to explore any associations with antipsychotics or other psychotropic drugs. The deaths occurred between 1990 and 1998, when conventional antipsychotic drugs accounted for the majority of prescriptions.

METHODS

We identified all New Zealand men and women aged 15–59 years who died between 1 January 1990 and 31 December 1998, where the underlying cause was

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certified as codes 415.1, 451 or 453 of the International Classification of Diseases (9th revision). Clinical information and names of general practitioners were obtained from coroners' and police records, death certificates and hospital records; when necessary, we also wrote to next of kin to ask for the name of the general practitioner. Of the 122 potential cases identified, 8 did not normally live in New Zealand, 9 had insufficient evidence for a diagnosis of pulmonary embolism and for 13, the pulmonary embolism was not the underlying cause of death (5 had advanced cancer, 7 had post-operative pulmonary emboli and 1 had portal vein thrombosis). The general practitioners of 2 of the 92 eligible cases could not be identified. For the others, general practitioners were asked if one of us (Lianne Parkin) could visit their practice and examine the records of the case and 4 controls. No doctor refused, but for 15 patients, the medical records had been lost. For the remaining 75, the diagnosis of pulmonary embolism was confirmed by necropsy in 69, by ventilation-perfusion scans or angiography in 3 and by two specialist clinicians (using standard criteria[5] and blinded to exposure status) in 3. The date of onset of the fatal episode was taken as an index date.

For each case, 4 controls, matched for sex and year of birth (except for 14 controls who were born in adjacent years to the cases), were selected from the group medical practice to which the case had belonged on the index date. The controls were selected randomly from an age-sex register in 71 practices (computerised in all except 1), from patient registration slips in 1 practice and by random selection of medical records in 3 practices. Potential controls were excluded if they were not normally residing in New Zealand or did not belong to the practice on the index date. Information about medical histories and drug exposures before the index date was abstracted from the records of general practitioners, psychiatric services and family planning clinics, using an identical approach for cases and controls. The date on which each patient had joined their general practice was recorded and because the records of many patients included information from practices to which they had previously belonged, the date of the earliest information was also noted.

Users of psychotropic drugs were defined as those who had been prescribed medication for at least 1 month. Current use was defined as prescribed use at any time during the 3 months before the index date. Psychotropic drugs were divided into three groups: antipsychotics, antidepressants and other psychotropics (a group including benzodiazepines and other anxiolytics, lithium carbonate, carbamazepine, sodium valproate and zopiclone). Antipsychotic agents were classified according to potency, that is, the dose of the drug required to achieve a therapeutic effect.[6–9] In matched analyses, using conditional logistic regression (STATA v7.0), we estimated relative risks by calculating odds ratios and 95% confidence intervals. We adjusted for weight (four categories, including missing values, for both sexes) and combined oral contraceptive use and hormone replacement therapy within 3 months of the index date. Because conditional logistic regression can give misleading estimates with small numbers, we checked the analyses with unconditional logistic regression, adjusting for the matching factors. The association between psychotropic drug use and fatal pulmonary embolism was examined for all subjects, although the key analyses were restricted to those without major risk factors for venous thromboembolism. The latter group is regarded as the most informative for studying adverse effects of medicines. Ethical approval for the study was granted by each of the regional ethics committees.

RESULTS

Of the 75 cases, 51 were female (median age 43.0 years) and 24 were male (median age 49.5 years). The mean times that cases and controls had been members of their practices were 9.9 years (standard error [SE] = 1.0) and 8.7 (SE = 0.6) years, respectively. The difference was not statistically significant ($p = 0.2$). The mean number of years of recorded medical information was 13.5 (SE = 1.2) for cases and 12.2 (SE = 0.6) for controls. Again the difference was not statistically significant ($p = 0.2$).

Ten cases and 2 controls had a past history of venous thromboembolism. A further 3 cases had a severe injury or prolonged immobility in the 2 months before the index date; while 3 controls were pregnant and 1 had major surgery during the same period. All of these people were classified as having major risk factors for venous thromboembolism. The following presentation of results will focus on people without major risk factors, although the tables also include results for all subjects.

Of the 62 cases without major risk factors, 43 were female (median age 42.0 years) and 19 were male (median age 47.0 years). Eight cases and 2 controls were current users of antipsychotics (Table 1). Thioridazine, a low potency antipsychotic, was used by 6 cases and 1 control. High potency antipsychotics were used by 2 cases (haloperidol) and by 1 control (prochlorperazine). There were no users of atypical agents. All users, except for the control who was

Table 1. Current use of antipsychotics

	Cases (exposed/total)	Controls (exposed/total)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Any antipsychotic†				
All subjects	9/75	3/300	12.0 (3.2–44.3)	9.7 (2.3–40.9)
Subjects without major risk factors for VTE‡	8/62	2/243	16.0 (3.4–75.3)	13.3 (2.3–76.3)
Low potency antipsychotic†				
All subjects	7/75	1/300	28.0 (3.4–227.6)	29.3 (2.8–308.2)
Subjects without major risk factors for VTE‡	6/62	1/243	24.0 (2.9–199.3)	20.8 (1.7–259.0)

*Adjusted for weight (four categories, including missing values, for both sexes), combined oral contraceptive use and hormone replacement therapy during the 3 months before the index date.
†Non-users of antipsychotics (never and past-users combined) are the reference group.
‡No history of venous thromboembolism or of prolonged immobility, severe injury, major surgery or pregnancy during the 2 months before the index date.

prescribed prochlorperazine for labyrinthitis 6 weeks before the index date, had received antipsychotic medication either continuously or intermittently over many years. Four cases and 1 control had a diagnosis of schizophrenia noted in their records, while another case had a possible diagnosis of schizophrenia recorded. Of the remaining cases, 1 had a bipolar affective disorder, 1 had an intellectual disability and was prescribed thioridazine for behavioural control and 1 was taking thioridazine to treat insomnia. No user had an acute psychotic episode in the 3 months before the index date; 1 man was admitted to hospital following an overdose.

Taking non-users (never and past-users combined) as the reference group, the odds ratio (adjusted for weight, combined oral contraceptive use and hormone replacement therapy) for current use of antipsychotics was 13.3 (95% CI: 2.3–76.3). Low potency antipsychotics carried the highest risk, with an adjusted odds ratio of 20.8 (95% CI: 1.7–259.0). The increased risk of pulmonary embolism in users of any antipsychotic persisted when women who were current users of combined oral contraceptives or hormone replacement therapy were excluded from the analysis, with an odds ratio (adjusted for weight) of 8.3 (95% CI: 1.3–53.5). Although the odds ratio for past use of antipsychotics, compared with never use, was elevated, this was not statistically significant (adjusted odds ratio 5.3 [95% CI: 0.6–45.8]). The adjusted odds ratio for use of antipsychotic medication within 1 month of the index date was 11.2 (95% CI: 1.9–65.4). An unmatched analysis (adjusted for age, sex, weight, combined oral contraceptive use, hormone replacement therapy and clustered on practice) gave similar results to the matched analysis, with an odds ratio for antipsychotic use within 3 months of the index date of 14.1 (95% CI: 3.3–61.1).

When current users of antipsychotics were excluded, 6 cases and 7 controls without major risk factors for venous thromboembolism were current users of antidepressants (Table 2). Tricyclic antidepressants were used by 4 cases and 5 controls. One of these cases and 1 further case were taking a selective serotonin reuptake inhibitor; the other case was taking a monoamine oxidase inhibitor. Of the remaining controls, 1 was using a selective serotonin reuptake inhibitor, while the other was taking a monoamine oxidase inhibitor. None of the users had been admitted to hospital for depression during the 3 months before the index date, although 2 cases were diagnosed with acute depression and were prescribed tricyclics as outpatients about 2 months before the

Table 2. Current use of antidepressants

	Cases (exposed/total)	Controls (exposed/total)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Any antidepressant†				
All subjects	8/66	7/261	5.5 (1.8–17.1)	10.0 (2.4–41.2)
Subjects without major risk factors for VTE‡	6/54	7/209	3.7 (1.1–12.5)	4.9 (1.1–22.5)

*Adjusted for weight (four categories, including missing values, for both sexes), combined oral contraceptive use and hormone replacement therapy during the 3 months before the index date.
†Current users of antipsychotics are excluded. Non-users of antidepressants (never and past-users combined) are the reference group.
‡No history of venous thromboembolism or of prolonged immobility, severe injury, major surgery or pregnancy during the 2 months before the index date.

index date. Only 1 user, a control, was taking a tricyclic for a reason other than depression (migraine prophylaxis). Of the remaining users, 1 case first commenced treatment 9 months before the index date, while all the others had been taking antidepressants intermittently or continuously for years. With non-users as the reference group, the odds ratio (adjusted for weight, combined oral contraceptive use and hormone replacement therapy) for current use of antidepressants was 4.9 (95% CI: 1.1–22.5). The adjusted odds ratios for current and past use of antidepressants, compared to never use, were 6.3 (95% CI: 1.3–30.8) and 2.9 (95% CI: 0.7–11.5) respectively. An analysis including current users of antipsychotics, but adjusting for such use, also found an increased risk in current users of antidepressants (odds ratio 5.5 [95% CI: 1.3–23.8]).

There was no increased risk for current or past use of other psychotropic drugs as a group. When we excluded users of antipsychotics or antidepressants, the adjusted odds ratio for current use was 1.4 (95% CI: 0.3–7.7). Adjusting for antipsychotic and antidepressant use produced an identical point estimate (odds ratio 1.4 [95% CI: 0.3–5.8]).

DISCUSSION

This case-control study found that current users of antipsychotic drugs had an increased risk of fatal pulmonary embolism, when compared with non-users. Low potency antipsychotics carried the highest risk, with thioridazine being the main drug involved. The odds ratio for current use of antidepressants was also increased. The odds ratios for past use of antipsychotics and antidepressants were not significantly increased.

The study was population-based and it was possible to identify all cases of idiopathic fatal pulmonary embolism that occurred in New Zealand during the study period. Diagnostic bias was unlikely because most people who die unexpectedly in New Zealand are referred for necropsy. Information about drugs prescribed and medical history was derived from medical records and hence was not subject to recall bias. Controls were selected from the same general practices as cases and there was no significant difference in the mean time that cases and controls had been members of their practices or in the number of years of recorded medical information. The date of onset of the fatal episode (rather than the date of death) was taken as the index date, so the prescription of antipsychotic or antidepressant drugs for unrecognised early symptoms of venous thromboembolism is an unlikely explanation for our results. Moreover, most of the cases had been taking their medication for at least a year.

Confounding by sex, age, weight, concomitant drug use or underlying medical conditions is unlikely: controls were matched to cases for sex and year of birth; we adjusted for weight, use of combined oral contraceptives and hormone replacement therapy; and we excluded individuals with major risk factors from the key analyses. It was not possible to adjust for body mass index because the height of many patients was unrecorded, but it is unlikely that adjusting for weight instead of body mass index made a substantial difference to our results.

The number of cases was inevitably restricted by the size of the New Zealand population. This limited our capacity to examine a number of features—especially any association with classes of drugs other than antipsychotics and antidepressants. The general practice records of 15 cases could not be located, which might have biased our results. However, this was mostly due to practice-related reasons (such as doctors moving premises, retiring or dying) and it did not appear to be related to particular characteristics of cases.

Our finding of an increased risk of fatal pulmonary embolism in current users of conventional antipsychotics is consistent with previous studies of non-fatal venous thromboembolism.[1,2] Like Zornberg and Jick,[1] we found that users of low potency formulations carried the highest risk. The re-analysis of the Leiden Thrombophilia Study in the Netherlands found that 4 of the 474 cases with deep vein thrombosis and none of the matched controls, were current users of antipsychotics.[2] The findings of a Canadian cohort study were less consistent.[10] Using linked data from health care administrative records, Ray *et al.* compared the risk of venous thromboembolism in users of antipsychotic drugs and users of thyroid replacement hormone. An increased risk was found for users of butyrophenone antipsychotics only (adjusted relative risk 1.43 [95% CI: 1.18–1.74]). However, the study was confined to patients of age 65 years and more and diagnostic bias could not be ruled out since users of antipsychotics were older, were more likely to be living in long-term care facilities and may have been more cognitively impaired than the comparison group.

Information about antipsychotic use and fatal venous thromboembolism is limited. Thomassen *et al.* reviewed necropsy reports at the Leiden University Medical Centre in the Netherlands.[2] Ten of the 27 deaths from idiopathic pulmonary embolism occurred in psychiatric patients, 5 of whom were known users of antipsychotic drugs. In a case-control study of fatal

cardiovascular disease in women of childbearing age in England and Wales, Thorogood *et al.* unexpectedly found an increased risk of myocardial infarction in users of psychotropic drugs, particularly tricyclic antidepressants and benzodiazepines.[11] An almost threefold increased risk of pulmonary embolism in current users of psychotropics was also observed, although no estimates were reported for individual drug groups. Walker *et al.* linked data from a national registry of clozapine users with death registrations in the United States.[3] Among those aged 10–54 years, the standardised mortality rate for pulmonary embolism in current users was five times that of past users (relative risk 5.2). This may be a conservative estimate since patients who were classified as past users of clozapine could have been taking other antipsychotics.

Antipsychotic drugs have also been implicated in sudden cardiac death[12] and it is possible that deaths from pulmonary embolism could be misclassified as due to myocardial infarction or arrhythmia when necropsies are not performed. For example, in a recent case-control study, thioridazine was identified as a risk factor for sudden unexplained death among psychiatric inpatients (adjusted odds ratio 5.3 [95% CI: 1.7–16.2]).[13] Drug-induced arrhythmia was thought to be the most likely cause. Since a necropsy was performed in only 36% of the cases, the possibility that some of the remaining patients died from pulmonary embolism cannot be ruled out. Interestingly when the analysis was confined to patients who had undergone a necropsy, a significant association between thioridazine and sudden unexplained death was not found (adjusted odds ratio 2.9 [95% CI: 0.7–11.7]).

The previous evidence of an increased risk of non-fatal venous thromboembolism in antipsychotic users tends to argue against differential survival as an alternative explanation for our results. Moreover, the absence of a significantly increased risk for past use in our study is consistent with the hypothesis that the drugs, rather than any underlying characteristics of the people who used them, were responsible for the increased risk among current users. Nevertheless, the estimate for past use was elevated, with a wide confidence interval, so the possibility that people who are considered to need these drugs carry some increased risk cannot be ruled out. Earlier studies that found significantly elevated risks for current users of conventional[1] and atypical[3] antipsychotics, took past users as the reference group. This provided some control for the underlying condition, but it did not permit the evaluation of a possible increased background risk in users of antipsychotic drugs.

There is no clear explanation for the increased risk of venous thrombosis in users of antipsychotics. Several hypotheses have been proposed, including enhanced aggregation of platelets,[1] anticardiolipin antibodies,[1] exacerbation of venous stasis during sedation,[1] increased adrenaline secretion in the acute psychotic phase[2] and hyperhomocysteinaemia.[10]

The observed association between current use of antidepressants and fatal pulmonary embolism was not expected, although it should be noted that tricyclic drugs closely resemble the phenothiazines chemically.[14] There have been isolated reports of venous thromboembolic events in users of antidepressants who were also immobilised[15] or concurrently using antipsychotics.[16] Zornberg and Jick found an odds ratio of 1.7 (95% CI: 0.8–3.7) for current use of antidepressants.[1] This result was based on only 3 exposed cases and 20 exposed controls, so it was not incompatible with our observation. In the re-analysis of the Leiden Thrombophilia Study, 9 cases and 4 controls were current users of antidepressants, giving an odds ratio for current use of 2.3 (95% CI: 0.6–10.2).[2] The adjusted relative risk for current use of antidepressants in the Canadian cohort study was 1.04 (95% CI: 0.94–1.15).[10]

If the association between antidepressant drugs and fatal pulmonary embolism is real, it needs to be established whether antidepressant drugs increase the risk of venous thromboembolism or whether the people with depression are more likely to die from the condition. Antidepressants are widely used and further studies are required to clarify the association between these drugs and venous thromboembolism.

KEY POINTS

- Compared to non-use, current use of conventional antipsychotics was associated with an increased risk of fatal pulmonary embolism (adjusted odds ratio 13.3 [95% CI: 2.3–76.3]).
- Low potency antipsychotics carried the highest risk (adjusted odds ratio 20.8 [95% CI: 1.7–259.0]).
- The odds ratio for current use of antidepressants was also increased (adjusted odds ratio 4.9 [95% CI: 1.1–22.5]).
- Current use of other psychotropic drugs was not associated with an increased risk.
- The findings for antipsychotics were consistent with previous studies, but the association between use of antidepressants and fatal pulmonary embolism was not expected and needs to be replicated.

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Air travel and fatal pulmonary embolism

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Summary
Although long-distance air travel is commonly regarded as a risk factor for venous thromboembolism, the risk of clinically important events has not been well defined. We estimated the absolute risk of dying from pulmonary embolism following long-distance air travel in a national population-based descriptive study of 121 men and women who were aged 15–59 years (the age range in which the majority of international arrivals are found) and whose underlying cause of death was certified as codes 415.1, 451, or 453 of the International Classification of Diseases (ninth revision). Eleven cases had undertaken long-distance air travel in the four weeks before the onset of the fatal episode. The estimated risks of fatal pulmonary embolism following a flight of at least three hours' duration were 0.5 (95% CI 0.2–1.2) and 0.6 (95% CI 0.2–1.4) per million arrivals for overseas visitors and New Zealand residents, respectively. For air travel of more than eight hours' duration, the risk in New Zealand residents was 1.3 (95% CI 0.4–3.0) per million arrivals. We also conducted a case-control study based on those cases who were normally resident in New Zealand and registered on the electoral roll (n=99). For each case, four controls matched for sex, age, and electorate, were randomly selected from the electoral roll. In the key analysis (based on 88 cases and 334 controls), the adjusted odds ratio for travellers who had flown for more than eight hours was 7.9 (95% CI 1.1–55.1) compared with those who did not undertake a long-distance flight. Long-distance air travellers have a higher risk of dying from pulmonary embolism than non-travellers, but the absolute risk in people aged 15–59 years appears to be very small.

Keywords
Clinical / epidemiological studies, pulmonary embolism

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Introduction

It is commonly believed that there is a link between air travel and venous thromboembolism (VTE) (1), but the risk has not been clearly defined (2). The relative risk of fatal events has not been examined and the only study to estimate pulmonary embolism mortality in air travellers linked Western Australian immigration and hospital admission data (3), thus excluding people who died in the community. We therefore conducted a national population-based study to estimate both the relative and absolute risks of fatal pulmonary embolism following long-distance air travel. There were two components to the research: a descriptive study of men and women who died from pulmonary embolism in New Zealand between 1990 and 2000, and a case-control study. The principal aims were to examine any association between long-distance air travel and the risk of dying from pulmonary embolism, and to estimate the absolute risk of death from pulmonary embolism in air travellers aged 15–59 years. A secondary objective was to compare the mortality rate from pulmonary embolism in a population in which almost all people had recently undertaken long-distance air travel (overseas visitors to New Zealand) with the rate in a population where few would recently have travelled (the resident population of New Zealand).

The relative geographic isolation of New Zealand makes it an ideal country in which to undertake such research. With the exception of flights from neighbouring Pacific Islands and the east coast of Australia (3–4 hour flights), and from other parts of Australia (5–8 hour flights), passengers arriving in New Zealand have all undertaken journeys with flight times of more than eight hours, and in many cases more than 24 hours.

Descriptive study

Materials and methods

Selection of cases

The New Zealand Health Information Service (NZHIS) identified all New Zealand residents and overseas visitors aged 15–59 years who died in New Zealand between 1 January 1990 and 31

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December 2000, for whom the underlying cause of death was coded to one of the following rubrics of the ninth revision of the International Classification of Diseases (ICD): 415.1 (pulmonary embolism and infarction), 451 (phlebitis and thrombophlebitis), or 453 (other venous embolism and thrombosis). People for whom the underlying cause was coded as rubrics 451 or 453 were included in the study only if there was clear evidence that distal venous thrombosis had been complicated by pulmonary embolism. The research was confined to people aged 15–59 years because the majority (77%) of people who arrived in New Zealand on international flights during the study period were within this age range (data provided by Statistics New Zealand).

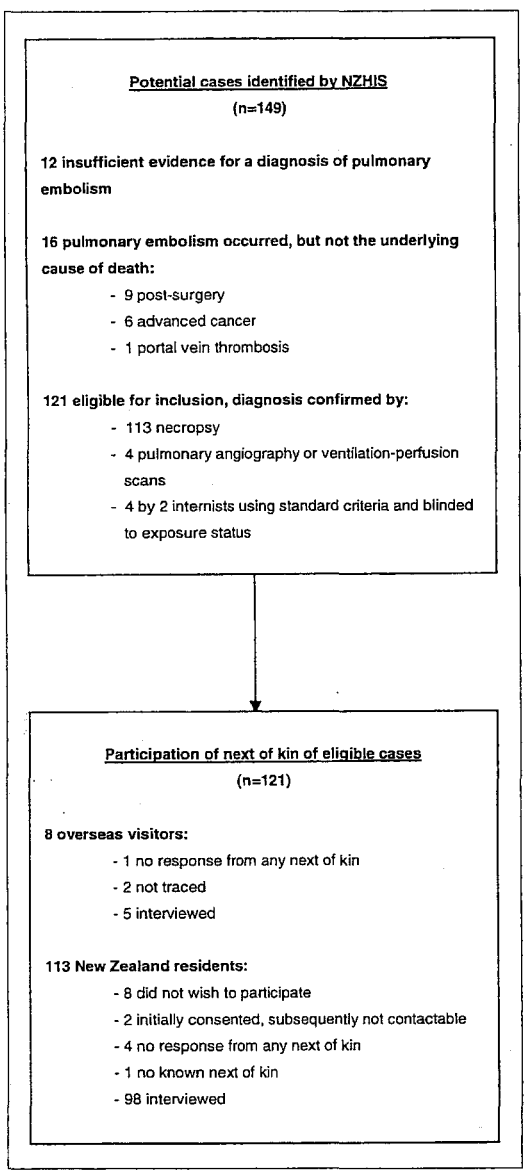

Figure 1: Descriptive study: participation of next of kin.

We sought clinical information and names of the next of kin from death certificates and from coroners', police, hospital, general practice, mental health, and family planning records. The clinical information obtained included the circumstances of the fatal episode, reported symptoms, the results of any physical examination and diagnostic tests, necropsy findings, as well as details about medical history and medication use. The date of onset of the fatal episode was taken as an index date. Of 149 potential cases identified, 121 were eligible for inclusion in the study (Fig. 1). The diagnosis of pulmonary embolism was confirmed by necropsy in 113 and by ventilation-perfusion scans or pulmonary angiography in four. Of the remaining four cases, two had venograms that demonstrated venous thrombosis. Two specialists in internal medicine, using standard criteria (4) and blinded to exposure status, determined that these four cases also had sufficient evidence for a diagnosis of pulmonary embolism.

Definition of long-distance air travel

In both the descriptive and case-control studies, we defined long-distance air travel as a flight of at least three consecutive hours. This allowed comparisons with the studies that had been published at the time the study was initiated (5–7). Furthermore, since domestic air travel within New Zealand involves flight times of less than three hours while international flights to and from New Zealand involve journeys of at least three hours' duration, such a definition simply required study participants to recall any international travel during the relevant period. Such travel could often be verified by reference to passports and other personal records. For similar reasons, any domestic flights within countries other than New Zealand that had involved flight times of more than three hours would probably be identified.

Estimation of absolute risks

For each person who died from pulmonary embolism, we sought information about long-distance air travel in the four weeks before the date of onset from medical and death records and from next of kin (discussed below). The 4-week period was chosen to allow comparisons with previous studies (5–8).

The numbers of New Zealand residents and overseas visitors arriving in New Zealand on international flights, by sex and 5-year age groups, in the years 1990 to 2000 were provided by Statistics New Zealand. These data were derived from analyses of the arrival cards which all travellers arriving in New Zealand are required to complete. Because travellers are asked to record only the airport from which their last flight departed, these data provided insufficient information about the total duration of air travel undertaken by arriving passengers. Therefore, we used information from the control series in the case-control study (see below) to estimate the number of arrivals by New Zealand residents following air travel of more than eight hours during the same period. The proportion of controls who had undertaken a journey with a total flight time of more than eight hours in the four weeks

before the index date was multiplied by 13 (to estimate the proportion over one year) and the product multiplied by the annual estimates of the New Zealand population aged 15–59 years to calculate the number of arrivals by New Zealand residents on flights of more than eight hours in the years 1990 to 2000. To assess the validity of this approach, we also estimated the number of arrivals on flights of any duration and compared this figure with the arrivals data provided by Statistics New Zealand.

Comparison of mortality rates in overseas visitors and New Zealand residents

The numbers of deaths from all causes in New Zealand residents and overseas visitors by sex and 5-year age groups for the years 1990–1998 were obtained from NZHIS. Data for 1999 and 2000 were not available for all-cause deaths because the country of usual residence was not coded in these years. Existing records were used to determine whether people who died from pulmonary embolism in 1999 and 2000 had been resident in New Zealand or overseas.

Statistics New Zealand provided the number of New Zealand residents within each sex and 5-year age group (based on quinquennial census counts and adjusted for net migration and deaths) for each year of the study period. Corresponding data for overseas visitors were derived by linear interpolation between census counts. Because seasonal trends were evident in the monthly overseas visitor arrival data, the census counts and estimated population in non-census years were seasonally adjusted. Sex and age-specific population data for New Zealand residents and for overseas visitors were added together to calculate the person-years of observation in residents and visitors for the relevant periods. In the years 1990 and 2000, the total resident population of New Zealand was 3,379,250 and 3,832,930, respectively.

We used direct and indirect methods of sex and age standardisation to compare mortality rates for pulmonary embolism and all causes in the overseas visitor population with the rates in the New Zealand resident population (9). The Poisson distribution was used to compute 95% confidence intervals (95% CI) for adjusted rate ratios, standardised mortality ratios, and absolute risks.

Results

Deaths from pulmonary embolism

Of the 121 deaths, 113 occurred in people who were usually resident in New Zealand on the index date and eight were in overseas visitors. Eighty were female (median age 43.1 years) and 41 were male (median age 49.0 years). Eleven people (9.1% of deaths) had undertaken long-distance air travel in the four weeks before the index date. These comprised five residents and six overseas visitors.

The characteristics of the people who died after long-distance air travel are shown in Table 1.

One person had undertaken three long-distance journeys during the relevant period, and two others had flown on two separate occasions. The remaining cases flew only once in the four weeks before the index date, although two undertook further air travel after the onset of symptoms. Nine (five residents and four visitors) of the 11 air travellers had undertaken journeys with total flight times of more than eight hours. Seven travelled in economy class, one had undertaken two flights in economy class and one in business class, and for three cases the class of travel was not determined. None were reported to have taken hypnotic drugs immediately before or during air travel. For nine people, symptoms of VTE developed within eight days of air travel. Only two of the air travellers were admitted to and died in hospital, two others died on arrival at hospital emergency departments, and seven died in the community.

Table 1: Characteristics of cases who undertook long-distance air travel in the four weeks before the onset of their fatal episode.

Case *	Sex	Age (years)	History of VTE	BMI † (kg/m^2)	Other risk factors for VTE ‡	Family history of VTE
1	Female	47	No	34.9	Norethisterone Medroxyprogesterone acetate Tranexamic acid	No
2	Female	51	DVT in pregnancy	„rather obese" („average")	History of varicose veins	1 uncle, 3 cousins
3	Female	58	No	21.6	History of varicose veins Hormone replacement therapy	No
4	Male	36	No	31.2	Nil	No
5	Male	49	No	34.3	Paraplegia 33 years	No
6	Female	42	No	„well-built" (26.1)	Nil	No
7	Female	47	No	43.6	Nil	No
8	Female	54	Unknown	Unknown	Unknown	Unknown
9	Female	57	Unknown	30.4	Nil reported to airport medics	Unknown
10	Male	32	Injury-related DVT	„well-nourished" (28.9)	Nil	1 aunt
11	Male	39	No	24.2	Nil	No

* Cases 1–5 were usually resident in New Zealand on the index date, cases 6–11 were overseas visitors. Information about cases 8 and 9 was obtained from coroners' and hospital records only, as next of kin were not traced. † Pathologists' comments and BMI calculated from weight and height at necropsy. Next of kin comments and BMI calculated from reported weight and height are shown in parentheses. ‡ Information was sought about major risk factors for VTE in the three months before the index date (including surgery, major injury, prolonged immobility, pregnancy, hospital admissions for other reasons, hormone replacement therapy, and the use of oral contraceptives, psychotropic drugs, and other medications), varicose veins, known thrombophilia, systemic lupus erythematosis, inflammatory bowel disease, other medical conditions, ethnicity, and smoking.

Table 2: Absolute risks of dying from pulmonary embolism following long-distance air travel.

Exposure	Number of deaths among international arrivals aged 15–59 years, 1990–2000	Number of international arrivals aged 15–59 years, 1990–2000	Absolute risk per million international arrivals* (95% CI)
Overseas visitors, air travel ≥3 hours	6	11,224,909†	0.5 (0.2 – 1.2)
New Zealand residents, air travel ≥3 hours	5	8,100, 951†	0.6 (0.2 – 1.4)
New Zealand residents, air travel ≥3 hours	5	8,675,292‡	0.6 (0.2 – 1.3)
New Zealand residents, air travel >8 hours	5	3,855,960‡	1.3 (0.4 – 3.0)

*The absolute risks were obtained by dividing the number of deaths from pulmonary embolism among arrivals aged 15–59 years on international flights between 1990 and 2000 by the number of passengers of the same age who arrived during the same period. †Number of arrivals provided by Statistics New Zealand. ‡Estimated number of arrivals based on data from the case-control study.

Table 3: Mortality from pulmonary embolism and from all causes in the overseas visitor and New Zealand resident populations.

Cause of death	Mortality rate in overseas visitor population* (per million person-years)	Mortality rate in New Zealand resident population (per million person-years)	Adjusted rate ratio (95% CI)
Pulmonary embolism	19.70	4.56	4.32 (3.94 – 4.72)
All causes	1465.83	2022.42	0.72 (0.71 – 0.73)

*Standardised to the sex and age distribution of the New Zealand resident population.

Absolute risks

The risks of developing fatal pulmonary embolism in the four weeks following long-distance air travel are shown in Table 2. Using Statistics New Zealand arrival data as the denominator, the risks following a flight of at least three hours' duration were 0.5 (95% CI 0.2–1.2) and 0.6 (95% CI 0.2–1.4) per million arrivals for visitors and residents, respectively.

Using arrival estimates based on exposure data from controls in the case-control study as the denominator, the risk in residents following air travel of more than eight hours' duration was 1.3 (95% CI 0.4–3.0) per million arrivals.

Pulmonary embolism and all-cause mortality rates

The mortality rate from pulmonary embolism in overseas visitors was higher than the rate in the New Zealand resident population (Table 3); the sex and age-adjusted mortality rate ratio was 4.3 (95% CI 3.9–4.7) and the standardised mortality ratio (SMR) was 3.8 (95% CI 1.6–7.4). This is consistent with an increased risk of pulmonary embolism in air travellers, since almost all overseas visitors arrive by air and most remain in New Zealand for less than 30 days (10), while only a small proportion of the resident population undertakes international air travel during a 4-week period. The results are particularly striking, given that there appears to be a "healthy traveller" effect: the adjusted mortality rate ratio and SMR for deaths from all causes in overseas visitors were 0.72 (95% CI 0.71–0.73) and 0.71 (95% CI 0.64–0.76), respectively.

Case-control study

Materials and methods

Selection of cases

The case-control study was based on a subset of the 121 cases identified in the descriptive study. We excluded the eight overseas visitors as it was not possible to identify and contact members of an appropriate comparison group. For the same reason, 14 residents who were not registered on the New Zealand electoral roll on the index date were also excluded. Thus 99 cases were considered eligible for inclusion in the case-control study.

Selection of controls

For each eligible case, four controls matched by individual year of age, sex, and electorate were selected randomly from the electoral roll. People who were not usually resident in New Zealand / or not registered in the appropriate electorate on the index date were excluded, as were those not born within one year of their case. Those who did not meet the eligibility criteria could not be traced, or did not consent to be interviewed were replaced. Potential controls who did not wish to participate were asked if they were willing to answer three questions to establish eligibility.

Contacting participants

A letter was sent to potential controls and the next of kin of eligible cases, inviting them to take part in the study, and to return a form with contact details. Subsequently, oral consent was sought for a telephone interview. In situations where next of kin had died, could not be traced, or did not respond to three letters of invitation, other relatives were contacted.

The interview

Computer-assisted telephone interviews of next of kin and controls were all undertaken by a registered nurse or one of us (LP), using a standardised questionnaire. To assist recall about events before the index date, participants were sent a life-events calendar with the invitation letter and this was referred to during the interview. Participants were asked to check passports or other records before they answered questions about air travel in the four weeks before the index date. For long-distance air travellers, we enquired about the class of travel, whether the passenger had sat in an aisle seat, and the use of hypnotics. Permission was obtained from controls to check the dates of any hospital admissions before the index date. This information was already available for cases.

Body mass index (BMI) was calculated from the reported weight and height on the index date, and was classified as underweight (< 20 kg/m^2), normal weight (20 to < 25 kg/m^2), overweight (25 to < 30 kg/m^2), and obese (≥ 30 kg/m^2). Three controls and the next of kin of 26 cases were unable to provide an estimate of weight or height on the index date. For these people, the BMI

category was assigned using narrative comments about weight in relation to height. The New Zealand Socio-Economic Index 1996 (11) was used to classify socio-economic status. For people living with a partner or parents, the highest score in the household was taken.

The case-control study was based solely on data obtained during telephone interviews and the confirmation of hospital admission dates. No information about cases derived from other sources was used for comparisons between cases and controls.

Statistical methods

Conditional logistic regression was used to perform matched analyses using SAS (version 8). The exposures of any long-distance flight and flight times of greater than eight hours were modelled separately. The key analyses were restricted to persons who did not have advanced cancer, were not pregnant, and had not undergone major surgery (since the selection of cases excluded patients with these conditions). Unadjusted and adjusted odds ratios are reported, with confounders chosen using backwards selection and confirmed in univariate analyses.

Results

The participation of next of kin and controls is shown in Figure 2. One case was reported by relatives to have undergone surgery following major injury in the three months before the index date. Although this was not confirmed by hospital or necropsy records, we excluded this person from the case-control study since we did not have full access to the hospital records of the controls who reported surgery. Twenty-two controls were excluded from the key analyses: three had a history of cancer (excluding localised malignant melanoma), a further two had undergone major surgery in the three months before the index date, 13 were pregnant, and four were matched to the excluded case.

The characteristics of cases and controls are shown in Table 4. There were almost twice as many female cases as male, and the female cases were younger. Cases were more likely than controls to be obese, to have a past history of VTE, and to belong to the lowest socio-economic group. Cases were also more likely to have been admitted to hospital, have been immobilised, and have used oral contraceptives and antipsychotics in the three months before the index date. During this period, cases and controls had similar rates of smoking and use of hormone replacement therapy and aspirin. One case and no controls were reported to be taking an anticoagulant (warfarin). Similar proportions of cases and controls had a history of varicose veins and a family history of VTE. The ethnicity of subjects did not differ appreciably between the case and control groups.

Five cases and nine controls had undertaken at least one long-distance flight in the four weeks before the index date (Table 5). All of the cases and four of the controls had undertaken journeys with total flight times of more than eight hours. There were no additional cases or controls who had undertaken domestic flights within a country other than New Zealand during the relevant period. The median ages of the cases and controls who flew long-distance were 49.0 years and 52.5 years, respectively.

Taking those who had not flown as the reference group, the odds ratio (adjusted for a past history of VTE, for the BMI category, and for prolonged immobility, a hospital admission owing to a medical condition, combined oral contraceptive, or antipsychotic use in the three months before the index date) for a flight of at least three hours' duration was 1.8 (95% CI 0.5–7.1). For flight times of more than eight hours, the adjusted odds ratio was 7.9 (95% CI 1.1–55.1). Socio-economic status did not confound the association. We obtained a similar point estimate when we excluded people with a past history of VTE, or of major injury or prolonged immobility in the three months before the index date. The odds ratio (adjusted for the BMI category, and for any hospital admission owing to a medical condition, combined oral contraceptive, or antipsychotic use in the three months before the index date) for all air travel of more than eight hours was then 7.1 (95% CI 0.8–64.1). Excluding controls who were not in New Zealand on the date of death of their case (n=2) had minimal impact on the results.

Discussion

In the case-control study, people who had undertaken air travel of more than eight hours' duration were estimated to have an 8-fold increased risk of fatal pulmonary embolism compared with people who had not undertaken such a journey. This is consistent with the findings of the descriptive study from which, allowing for a "healthy traveller" effect, a 6-fold increase in risk can be estimated. In

Table 4: Characteristics of cases and controls.

Characteristic	Cases (n=88)	Controls (n=334)*
Sex (no [%])		
Male	30 (34.1)	120 (35.9)
Female	58 (65.9)	214 (64.1)
Age (years, median)		
All	45.5	47.1
Male	50.8	50.4
Female	42.6	43.0
BMI (no [%])		
<20	7 (8.0)	26 (7.8)
20–24	31 (35.2)	153 (45.8)
25–29	21 (23.9)	104 (31.1)
≥30	28 (31.8)	51 (15.3)
Did not answer question	1 (1.1)	0
Reported history (no [%])		
Venous thromboembolism	16 (18.2)	9 (2.7)
Varicose veins	23 (26.1)	80 (24.0)
Risk factors in 3 months before index date (no [%])		
Major fracture	0	3 (0.9)
Major injury	1 (1.1)	1 (0.3)
Hospital admission for other reasons	9 (10.2)	4 (1.2)
Prolonged immobility	8 (9.1)	3 (0.9)
Medication use in 3 months before index date		
Antipsychotic (no [% total])	6 (6.8)	3 (0.9)
Combined oral contraceptives (no [% female])	22 (37.9)	41 (19.2)
Hormone replacement therapy (no [% female])	4 (6.9)	17 (7.9)

*Eighteen controls are excluded: three had a history of cancer, two had surgery, and 13 were pregnant in the three months before the index date.

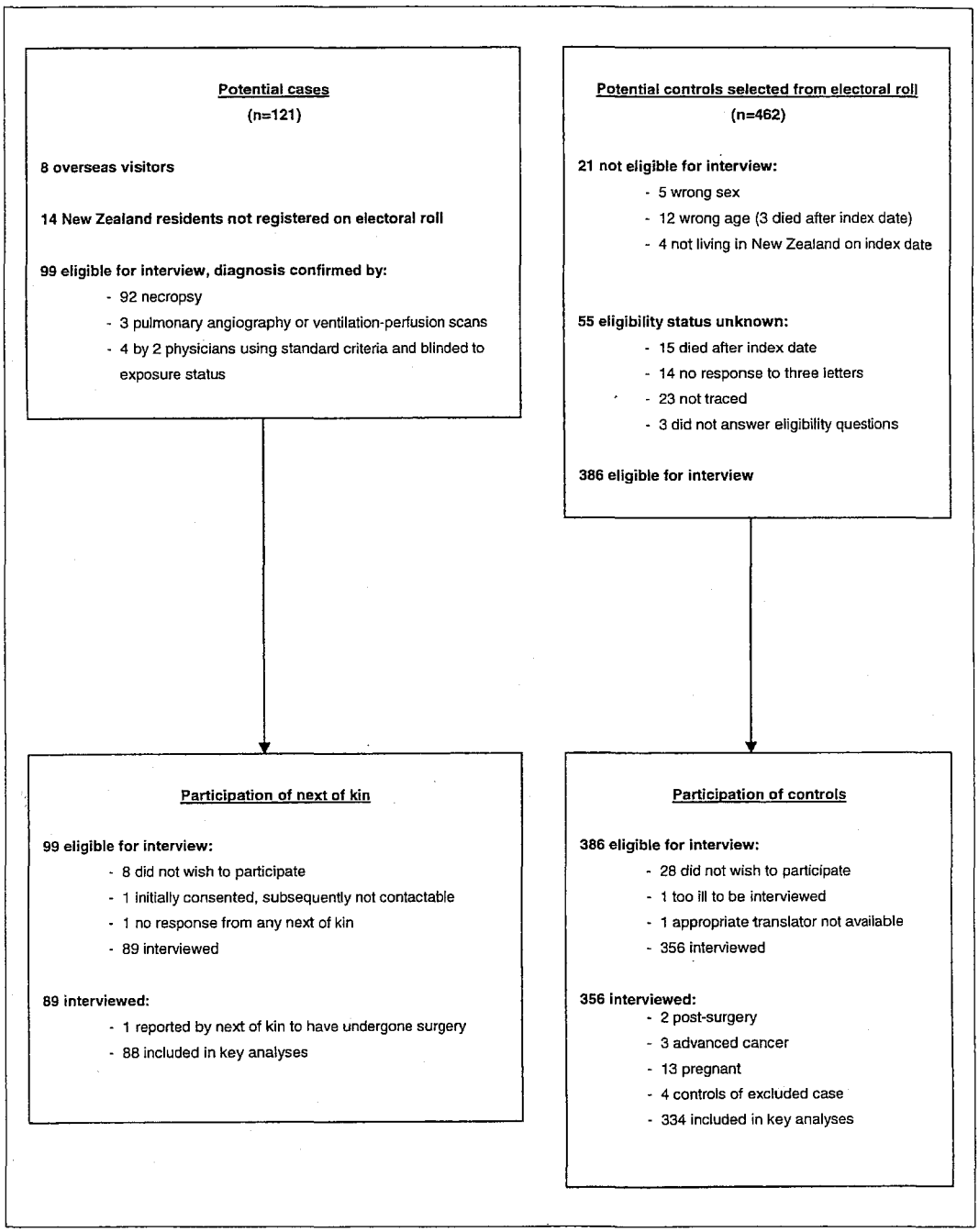

Figure 2: Case-control study: participation of next of kin and controls.

absolute terms, however, the risk of dying from pulmonary embolism after long-distance air travel appears to be very low. In this population-based research we were able to include all deaths that occurred in New Zealand during the study period for which pulmonary embolism was considered the underlying cause. In almost all cases the diagnosis of massive pulmonary embolism was confirmed by necropsy or other objective investigations. It is unlikely that we missed any relevant deaths because legal requirements to identify the cause of death (12) mean that almost all people aged 15–59 years who die unexpectedly in New Zealand are referred for necropsy, generally at the request of a coroner. Any air travellers who died en-route to New Zealand would also have been identified, except in situations where the aircraft did not proceed as intended. Because we studied fatal events, and because we included cases that occurred before widespread media publicity about a possible link between long-distance flights and VTE, referral bias is also unlikely to have influenced our results.

The response rates of next of kin in the descriptive and case-control studies were high (85.1% and 89.9%, respectively). The response rate of potential controls lay between 80.7% and 92.2%, since it is unlikely that everyone for whom eligibility status was not determined would have been eligible. It is also possible that potential controls who died after the index date, or could not be traced or contacted, were less likely to have undertaken long-distance air travel because of illness or because they belonged to a lower socio-economic group. Thus, any selection bias would tend to weaken the association between air travel and pulmonary embolism. It appears, however, that the control group gave a reliable estimate of exposure in the population that gave rise to the cases, since the estimated number of arrivals based on the proportion of exposed controls was very similar to the number of arrivals identified in official migration data.

The use of a standardised questionnaire minimised any potential for interviewer bias. Next of kin and controls were not informed of the study hypothesis, nor were the controls told about the condition being studied until their interview was completed. The use of passports and other records to confirm travel details helped to ensure that accurate information about air travel as far back as 1990 was obtained. All long-distance flights reported by next of kin in the descriptive study were confirmed by medical and death records.

Confounding by sex, age, proximity to an international airport, BMI, concomitant drug use, or an underlying medical condition is an unlikely explanation for our findings in the case-control study. Controls were matched to cases by sex, age, and electorate; we adjusted for a past history of VTE, BMI category, and for hospital admissions, prolonged immobility, oral contraceptive use and antipsychotic use in the three months before the index date; and we excluded individuals with a history of cancer, surgery or pregnancy in the three months before the index date. Temporal changes in travel patterns are also an unlikely explanation because controls were asked about air travel during the same calendar period as their cases.

There are several limitations to our research. Because fatal pulmonary embolism is a rare condition, there were only 121 deaths over an 11-year period among people aged 15–59 years in which pulmonary embolism was considered the underlying cause. Of these, 98 were identified as being eligible for inclusion in the case-control study and the next of kin of 88 were interviewed. This limited the precision of our estimates of relative risk, as demonstrated by the wide 95% confidence intervals. While use of proxy respondents for cases could have introduced some bias, we were able to verify dates of hospital admissions for both cases and controls, and we tested the reliability of information provided by next of kin by comparing it with information from other sources.

Table 5: Odds ratios of fatal pulmonary embolism in the four weeks following long-distance air travel.

Flight details	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
No long-distance flight	83	325	1.0	1.0
Air travel ≥ 3 hours	5	9	2.2 (0.7 – 6.8)	1.8 (0.5 – 7.1)
No long-distance flight	83	325	1.0	1.0
Air travel > 8 hours†	5	4	6.0 (1.4 – 25.4)	7.9 (1.1 – 55.1)

*Adjusted for past history of VTE, BMI (four categories), and for prolonged immobility (confined to bed or a wheelchair for more than a week), an admission owing to a medical condition, combined oral contraceptive, and antipsychotic use in the three months before the index date.
†Five controls who undertook air travel of eight hours or less excluded from analysis.

Because of the way in which mortality data were recorded during the study period, we were unable to identify all people for whom pulmonary embolism was the mechanism, although not the underlying cause, of death. Hence we could not estimate flight-related mortality rates in groups with predisposing conditions, in whom the risk of fatal pulmonary embolism following a long-distance flight is likely to be greater. Nevertheless, we did not study an entirely idiopathic group, since people with a personal history of VTE, a recent hospital admission, major injury, prolonged immobilisation or obesity, as well as users of oral contraceptives, hormone replacement therapy and antipsychotics, were included.

Our finding of an increased risk of fatal pulmonary embolism following long-distance air travel is consistent with the findings of some (3, 5, 7, 8, 13–18), but not all (6, 19), epidemiological studies of travel and non-fatal VTE. We found a similar magnitude of risk to that reported in two recent studies (3, 13). In a population-based case-control study in the Netherlands, air travel was associated with a 6-fold increased risk of non-fatal VTE (odds ratio 5.8 [95% CI 2.0–16.6]) (13). The Western Australian record-linkage study used a case-crossover approach to estimate the risk of being admitted to hospital with VTE following an international flight relative to the baseline risk (3). The relative risks of VTE in the first and second weeks after flying were 5.61 (95% CI 3.94–7.97) and 2.63 (95% CI 1.55–4.45), respectively. The risk was not elevated after a 14-day period. All of the flight-related cases in our case-control study developed symptoms of VTE within eight days of a journey of more than eight hours' duration.

There is evidence to suggest that flight-related VTE is most likely to occur in passengers with other risk factors (1, 7, 13, 14, 17). It was not possible to determine whether the cases and controls had prothrombotic mutations, and we were unable to examine the relative risk of fatal pulmonary embolism associated with

air travel in other subgroups, such as oral contraceptive users, since the number of cases was inevitably restricted by the size of the New Zealand population. Recent studies have found interactions between air travel, thrombophilia, and oral contraceptives. Air travellers with a prothrombotic mutation were reported to have a 13- to 16-fold increased risk of non-fatal VTE when compared with non-travellers without a mutation (13, 14), while current users of oral contraceptives who flew were reported to be 14 times more likely to develop non-fatal VTE than non-users who did not fly (14).

Assuming a case fatality rate of 2% (1), our estimates of pulmonary embolism mortality are higher than would be expected from studies of non-fatal cases referred to hospitals near airports (16, 18, 20), presumably because we were able to include all deaths that occurred in New Zealand in the days following long-distance air travel. In contrast, our estimates are much lower than would be expected from studies of asymptomatic VTE (15, 21–26) and from a study in which 1% of volunteers were reported to have developed symptomatic non-fatal VTE after a flight of at least 10 hours (27). The clinical relevance of asymptomatic VTE is unclear, and the latter study included subjects up to the age of 70 years and may have included a non-representative group of air travellers. Our findings confirm the dose-response relationship between the duration of travel and risk of VTE reported in previous studies (16, 18).

Our estimates of absolute risk following a flight of at least three hours are consistent with the estimate of 0.5 deaths per million arrivals reported in the Western Australian study (3), though the study groups were not strictly comparable. People who died in the community were excluded from that study, while our study suggests that most travel-related deaths occur outside hospital. Their inclusion of cases older than 59 years probably accounts for the similar estimate of risk.

In conclusion, while we confirmed that long-distance air travellers have a greater risk of dying from pulmonary embolism than non-travellers, we were reassured to find that fatal events were rare. Risks of the order of one in a million are much lower than recent publicity about the "economy class syndrome" has implied.

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